A Radical Approach to Nitrogen Heterocycles

by

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Dedicated to my family

with all my love and thanks

Contents

List of Figures

List of Tables

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Declaration

The work described in this thesis is the original work of the author and was carried out at the University of Warwick between October 1995 and February 1999. Full acknowledgement is made to all work and ideas included in this thesis but previously reported. This work has not previously been submitted for a degree at any institution.

Abbreviations

Ac	Acetate
ACN	Acetonitrile
AIBN	α, α'-Azo*iso*butyronitrile
Boc	*tert*-Butoxycarbonyl
Bn	Benzyl
Bz	Benzoyl
Cbz	Benzyloxycarbonyl
Cp	Cyclopentadienyl
DMF	N,N-Dimethylformamide
DCM	Dichloromethane
Et	Ethyl
Et_3N	Triethylamine
HRMS	High resolution mass spectrometry
Hz	Hertz
J	Coupling constant
LUMO	Lowest Unoccupied Molecular Orbital
Me	Methyl
mp	Melting point
m/z	Mass to charge ratio
PTOC	Pyridine-2-thione carbamate
*i*Pr	Isopropyl
SOMO	Singly Occupied Molecular Orbital
^{t}Bu	Tertiary butyl
TEA	Triethylamine
THF	Tetrahydrofuran
TLC	Thin layer chromatography
TMEDA	N,N,N'N'-tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	p-Toluenesulphonyl

Abstract

The generation of amidyl radical and carbon centred radicals using both tin hydride and non-tin hydride methods are described.

The effect of the nitrogen substituent upon the stereoselectivity of amidyl radical cyclisations onto the alkyl side chain using the tin hydride method was investigated. The O-benzoyl hydroxamic acid derivatives were chosen as precursors for these radicals. The results indicated that the *trans* isomers were the major isomers from the cyclisation reaction. The greatest diastereoselectivity was found when the nitrogen substituent was a methoxy group. However, the cyclisations afforded low yields of the desired sample products due to the difficulty in removing the tin residues from the crude.

Amidyl radicals were also generated from cyclohexadienyl functionalised hydroxamide acid derivatives using peroxides as initiators. Due to the rapid reduction of the amidyl radical by hydrogen abstraction from the initial cyclohexadienyl system under these conditions, the cyclisations were not successful.

The atom transfer radical cyclisation of allyl trichloroacetate was investigated. N-pentyl-2-pyridylmethanimine [164] was reported as an effective ligand in copper mediated cyclisation using Cu(I)Cl. The reaction was optimised in order to investigate the effect of ligand concentration, of catalyst concentration, of substrate concentration, and of solvent. It was found that two equivalents of ligand with CuCl provided the most effective catalyst while the use of 30mol% of catalyst was essential for the success of the cyclisation. A lower yield of product was obtained if the amount of catalyst was lowered and this may be due to its gradual decomposition. The reaction was best carried out at a concentration between 0.065 to 0.13M solution in order to suppress telomerisation processes and intermolecular addition and reduction processes due to hydrogen abstraction reactions. At higher concentrations more

telomers were obtained. In toluene solution, the CuCl-[164] catalyst system provided faster reactions when compared with the same reaction in acetonitrile solution.

The Cu(I)Cl-[164] was also used as an effective catalyst system for the atom transfer radical cyclisations of N-allyl trichloroacetamides. Intermolecular capture of cyclised radicals by a highly radicophilic reagent such as diphenyl diselenide was possible whereas the transfer of a cyano group by ethyl cyanoformate not. The cyclisation of tribromoacetamide derivatives using Cu(I)Br-[164] was also investigated. In addition, the effect of the structure of the ligand on the rate and diastereoselectivity of the cyclisation of N-allyl-N-tosyl dichloromethylacetamide was also studied. The cyclisation afforded the *trans* isomer as the major product. Ligands with more bulky N-substituents gave slower cyclisations and smaller diastereomer excesses.

Finally, the synthesis of medium-size lactams was investigated. Unexpectedly, attempts to synthesis the bigger ring lactams failed completely. The precursors underwent [1,5] aromatic rearrangement instead of cyclisation. In addition, the intramolecular 1,5 hydrogen abstraction of the starting amide radicals afforded significant amounts of reduced products.

CHAPTER 1

INTRODUCTION

1.1. Introduction

In recent years, the subject of free radical chemistry has grown enormously. Today radical intermediates are studied in every field of chemical activity, including organic, physical, inorganic and biological systems.[1] Since 1937 knowledge of organic reactions involving free radicals has increased steadily. The chief use of free radicals in organic synthesis is in synthetic methods such as halogenation, cyclisation and autoxidation processes. In addition many vinyl polymerisation processes are based upon free radical reactions.[2]

1.1.1. Definition of free radical

Free radicals have been defined as species which have one or more unpaired electrons.[2] In some cases, free radicals are monoatomic species such as the halogen atoms, the alkali metal atoms and certain metallic ions which have unpaired electrons. Some free radicals have the unpaired electron on a carbon atom, e.g. alkyl radicals. Most free radicals are too reactive to be isolated and they exist only as intermediates in various chemical reactions.

1.1.2. Reactions of free radicals

Most organic free-radical processes involve one or more of the following reaction types. The reactions can be classified either as radical-propagating reactions or radical-destroying reactions.[2,3] In propagation reactions, free radicals react either in a bimolecular reaction with a substrate molecule (e.g. atom or group transfer reactions, or addition and elimination reactions, or reduction reactions) or in unimolecular processes producing other free radicals (e.g. rearrangement reactions). Radical-destroying reactions are bimolecular reaction of two free radicals producing products that are not free radicals (e.g. coupling reactions and disproportionation reactions).

(I) Atom transfer reaction

This reaction is similar to the S_N2 reaction and is often referred to as S_R2 reaction. A free radical can attack an atom displacing a different free radical from this atom as shown in Scheme 1.1

$$A^{\cdot} + B{-}D \longrightarrow A{-}B + D^{\cdot}$$

Scheme 1.1

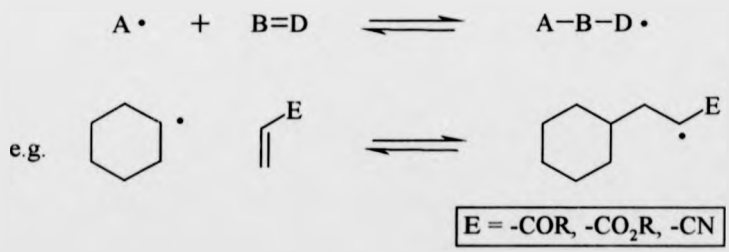
$A^{\cdot}$ is the attacking radical that displaces the radical $D^{\cdot}$ from B. This reaction is a radical-propagating reaction since one radical reacts with substrate producing another radical, e.g. the reaction of alkoxyl radicals with alkanes (hydrogen atom abstraction).

Scheme 1.2

The thermodynamically favoured formation of the strong O-H bond at the expense of the weaker C-H bond is the driving force for the reaction.

(II) Addition and Elimination reaction

In this reaction, free radicals add to the π-electron system of unsaturated compounds producing an adduct free radical (Scheme 1.3). This addition is often reversible.

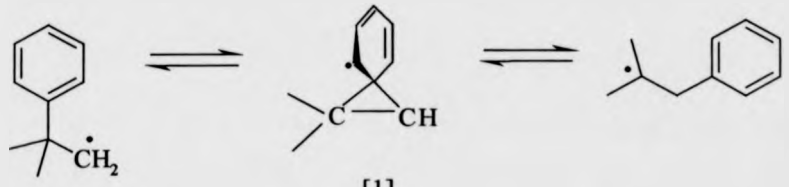


Scheme 1.3

The fragmentation reaction of an adduct radical is called β-elimination and furnishes the unsaturated compound and the adding free radical.

(II) Rearrangement reaction

A rearrangement is defined as intramolecular transfer of either an atom or group. This type of reaction is much less common in radical chemistry than for cationic chemistry. The aryl, vinyl, and acetoxy groups as well as halogen atoms appear to be most commonly involved in these migrations (Scheme 1.4).



[1]

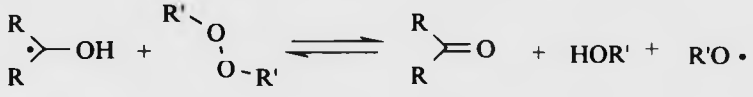
Scheme 1.4

In most cases for rearrangement to occur the group transferred must be unsaturated. The mechanism above involves two steps; cyclisation by intramolecular addition then re-opening of the ring with the cyclohexadienyl radical [1] as an intermediate.[4]

Similarly, halogen atoms can undergo 1,2 rearrangement *via* 3-membered ring intermediates. Generally, thermodynamic factors (i.e. the relative stabilities of the initial and rearrangement products) control the reaction.

(IV) Reduction reactions

Some free radicals have the ability to reduce a substrate by transfer of either a hydrogen atom or an electron to the substrate. For example, the reduction of peroxides by an α-hydroxyalkyl radical (Scheme 1.5).

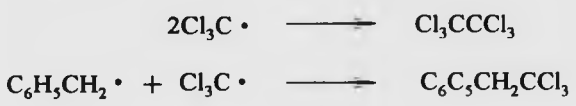


Scheme 1.5

The transfer of a hydrogen atom from an α-hydroxyalkyl radical to form the carbonyl function of a ketone is a reversible process and the position of the equilibrium depends on the stabilities of the two free radicals involved.

(V) Coupling reaction

This is a radical-destroying process which contrasts with the chain-propagation reaction just examined. Two free radicals which can be the same or different, can react with each other (Scheme 1.6).



Scheme 1.6

In this way, two unpaired electrons form a covalent sigma bond. This process is illustrated by the reaction of two trichloromethyl radicals and the cross-coupling of benzyl radical with the trichloromethyl radical.

(VI) Disproportionation reaction

This is the reaction between two radicals in which one radical is oxidised while the other is reduced, e.g. the reaction between two ethyl radicals producing ethylene and ethane (Scheme 1.7).

Scheme 1.7

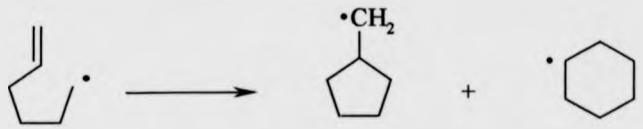
1.2. Carbon radicals

The use of carbon radicals in synthesis is attractive because carbon centred radicals can be generated under mild reaction conditions, show good regioselectivity in bond forming reactions, and do not react with many polar functional groups.[5] Recently, highly stereoselective and enantioselective[6] carbon radical mediated transformations have been reported. The methodology for formation of carbon radicals and their subsequent reactions has been reviewed[7] and the main method for their generation, a) the tin hydride dehalogenation and dechalcogenation methods, b) the addition-fragmentation method of allyl-tin compounds, c) the tris(trimethylsilyl)silane method, d) the thiohydroxamate ester method and e) the atom and group transfer methods will be discussed in more detail.

1.2.1. Chain reactions and synthetic planning

Most free radicals are highly reactive species. They react with themselves by combination or disproportionation at rates approaching the diffusion controlled limit. Therefore radical reactions involving chain reactions require low concentrations of radicals. A given chain reaction must generate radicals site-selectively and these radicals must have sufficient lifetime to react in the desired way to be useful in synthesis. However, this lifetime will be strictly controlled by the nature of the chain-transfer step.

Radical reactions are often highly regioselective, for example the hexenyl radical cyclisation illustrated in Scheme 1.8 which shows that addition to even unactivated alkenes can be effected. The protection of functional groups containing O-H or N-H bonds is not required, since these are among the strongest bonds to hydrogen found in organic molecules. Steric crowding, particularly on the radical centre, is often tolerated. For example, the *tert*-butyl radical adds to alkenes with rates faster than less substituted radicals because of their increased nucleophilicity. [8]



[2] [3] [4]

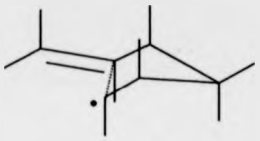
Scheme 1.8

From Scheme 1.8, hex-5-en-1yl radical [2] can cyclise to either the primary cyclopentylmethyl radical [3] or the secondary cyclohexyl radical [4]. It has been reported that the hex-5-en-1-yl radical cyclises predominantly to give the smaller five membered ring (*exo* cyclisation) rather than the larger six membered ring (*endo* cyclisation) in ratio 49:1.[4] The substantially greater yield of [3] which is the less stable product could be a result of the favorable activation ***enthalpy*** (eq. 1.1) rather than the activation ***entropy*** (eq. 1.2). [8]

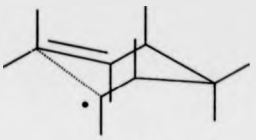
$$\Delta H^{\ddagger}_{1,6} - \Delta H^{\ddagger}_{1,5} = 1.7 \text{ kcal mol}^{-1} \qquad \text{eq. 1.1}$$

$$\Delta S^{\ddagger}_{1,5} - \Delta S^{\ddagger}_{1,6} = 2.8 \text{ kcal mol}^{-1} \qquad \text{eq. 1.2}$$

This regioselectivity, under enthalpy control, is explained by conformational and electronic effects. In the transition state, **A**, of the cyclisation to a 5-membered ring there is better SOMO (Singly Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) overlap than in transition state, **B**, to give 6-membered ring. [4]



A



B

In synthetic planing, the type of free radical reaction to be performed and the method of radical generation are important. A direct consequence of the use of chain reactions is the ability to conduct a series of reactive steps between radical generation and termination. Simply stated, the product of every radical propagation step is another radical. Thus several elementary steps may be involved in the conversion of A$^{\cdot}$ to B$^{\cdot}$

1.2.2. The Tin Hydride Method

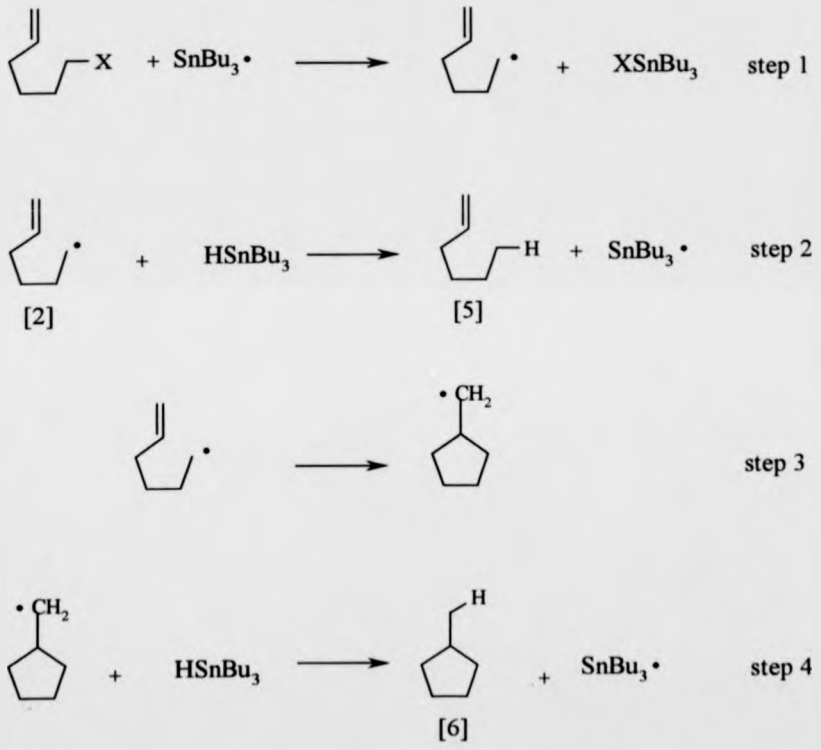
It was discovered in the mid-sixties that organotin hydrides were good reagents for the reduction of organic functional groups.[9] Recently, the use of organotin hydrides becomes the most important method for radical generation.[10] The most used tin hydride is tri-*n*-butyltin hydride (Bu_3SnH) which is used as the prototypical reagent for the generation of radicals. Bu_3SnH is easily prepared without special equipment and can be stored when pure for weeks or months. It can be prepared by the reduction of tri-*n*-butyltin chloride by lithium aluminium hydride or the reduction of bis-tri-*n*-butyltin oxide by borane.[11] Using Bu_3SnH, the radical generation from many functional groups can take place under mild conditions giving good yields of the desired products. The chain carrier, $Bu_3Sn^{\bullet}$, is generated in an initiation step (Scheme 1.9) from Bu_3SnH using azobisisobutyronitrile (AIBN) as a chemical initiator.

$$Bu_3SnH \xrightarrow{AIBN} Bu_3Sn\bullet$$

Scheme 1.9

The $Bu_3Sn^{\bullet}$ can then react further with other organic molecules. This is illustrated in scheme 1.10 by the reaction with hexenyl bromide. Initial attack of the precursor by $Bu_3Sn^{\bullet}$ generates the radical [2] which may either give the cyclic product [6] (Scheme 1.10). Reduction to [5] can be minimised by using low concentrations of Bu_3SnH.

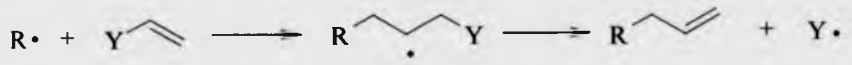
Syringe pump techniques for addition of the tin hydride can minimise the concentration of this reagent and offer a valuable alternative when slow cyclisations are involved. This can bypass the need for large solvent volumes. However, care must again be taken when low values of the rate constant for step 1 are anticipated. In such cases, significant concentrations of tin hydride could accumulate in the reaction medium before chain propagation became viable. [11]



Scheme 1.10

1.2.3. The Fragmentation Method

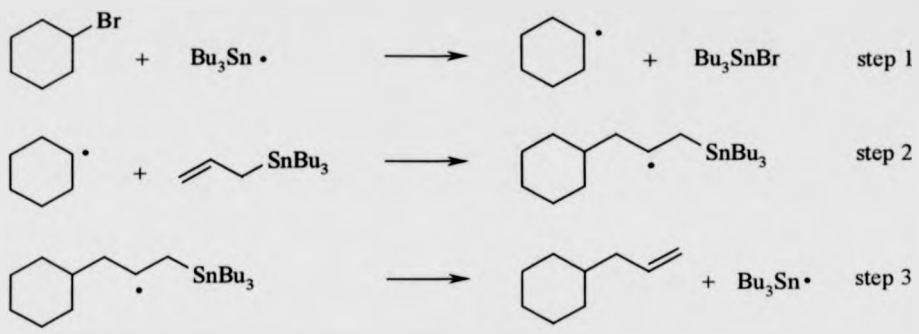
This method is a very powerful alternative way for generation of the chain-transfer agent. The generation reaction is shown in Scheme 1.11



Scheme 1.11

A radical Y is produced by rapid fragmentation of an appropriate C-Y bond. This radical may be the chain-transfer agent or may generate the chain-transfer reagent in a subsequent rapid reaction with a neutral molecule. The advantage of this approach is that the lifetime of intermediate radicals is not limited by the rate of hydrogen atom abstraction from a tin hydride source. Thus facilitating slow addition reactions.

An example of a free radical allylation with allyl stannanes is shown in Scheme 1.12.[12] The reaction can be initiated either thermally (with AIBN) or photochemically (with a tungsten lamp).



Scheme 1.12

Bromine abstraction provides the cyclohexyl radical and tin bromide. The cyclohexyl radical then adds to allylbutylstannane to produce β-stannyl radical which undergoes rapid fragmentation to provide allyl cyclohexane and regenerates the tri-*n*-butyltin radical. The requirement of this reaction sequence is that step 2 should be more rapid than decomposition/ removal of the cyclohexyl radical by other precursors.

1.3. Non-Tin Hydride methods

The literature survey showed that in the last few years, organotin hydrides such as tributyltin hydride have been used as free-radical mediators in a majority of radical reactions. However, the high toxicity of this reagent and the difficulty of removing it from the reaction products make it less than optimal. Recently, many research groups have developed alternative methods to generate radicals reductively.

1.3.1. Tris(trimethylsilyl)silane (TTMSS) method

Griller's group recently reported that the TTMSS can be used as an effecient free radical mediator due to the Si-H bond being considerably weaker than in simple silanes [13] It is has been found to be a very effective radical mediator with alkyl bromides and iodides, isocyanides, selenides and carbonyl derivatives.[14] TTMSS has a Si-H bond strength of 79 kcal mol^{-1}, which is very close to the Sn-H bond strength of 74 kcal mol^{-1} in Bu_3SnH.[15] The weaker bond strength of tris(trimethylsily)silane is probable due to the bonding interaction between β-silicon d orbitals and the semioccupied p orbital on the central atom in the corresponding silyl radical.[13] The non-toxic TTMSS is ecologically superior to tributyltin hydride and the ready purification of the products from the reduction mixture make it an attractive reagent. The mode of action of TTMSS to generate the desired reactive radicals is similar to that of tin hydride as shown in Scheme 1.13.

$$(Me_3Si)_3Si\text{-}H + In\bullet \longrightarrow In\text{—}H + (Me_3Si)_3Si\bullet$$

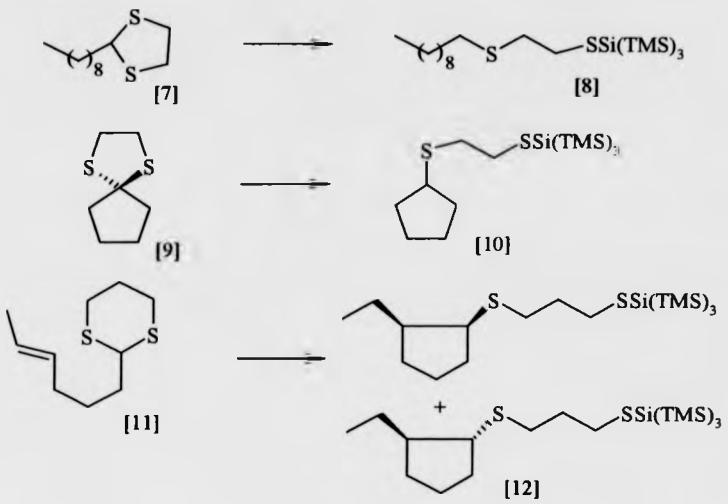
$$R\text{—}X + (Me_3Si)_3Si\bullet \longrightarrow R\bullet + (Me_3Si)_3Si\text{-}X$$

$$R\bullet + (Me_3Si)_3Si\text{-}H \longrightarrow R\text{—}H + (Me_3Si)_3Si\bullet$$

X = I, Br, SePh

Scheme 1.13

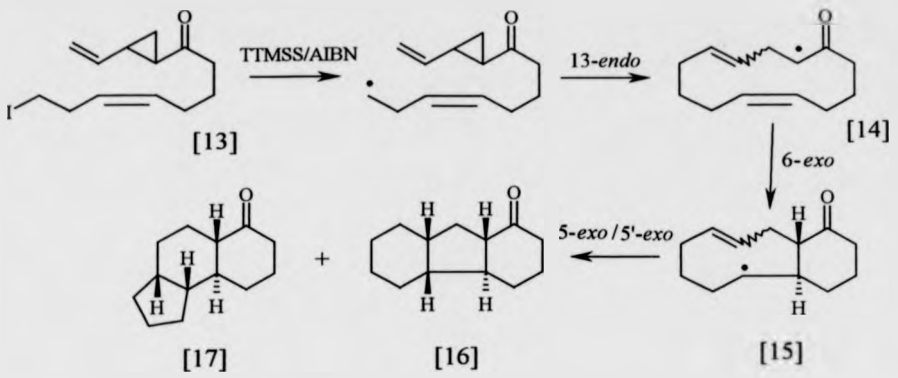
Arya and co-workers have demonstrated that TTMSS can cause selective cleavage of carbon-sulphur bonds.[15,16]



Scheme 1.14

Hence, when the 1,3-dithiolane of decanal [7] is treated with 1 equivalent of TTMSS in toluene using AIBN as an initiator at 85 °C cleavage of one of the carbon-sulphur bonds occurs to finish [8] in 87% yield. Similarly, the 1,3-dithiolane of cyclopentanone [9] undergo cleavage of one carbon-sulphur bond to give the thioether derivative [10] in 85%. Interestingly, the reaction of [11] furnishing the two diastereomeric cyclic products [12] as an inseparable mixture of 1:1 *cis* and *trans* isomers.

Recently, Pattenden and Wiedenau have described the stereoselective synthesis of various bicyclic and tricyclic carbo- and hetero-cyclic systems using TTMSS as mediator.[17]

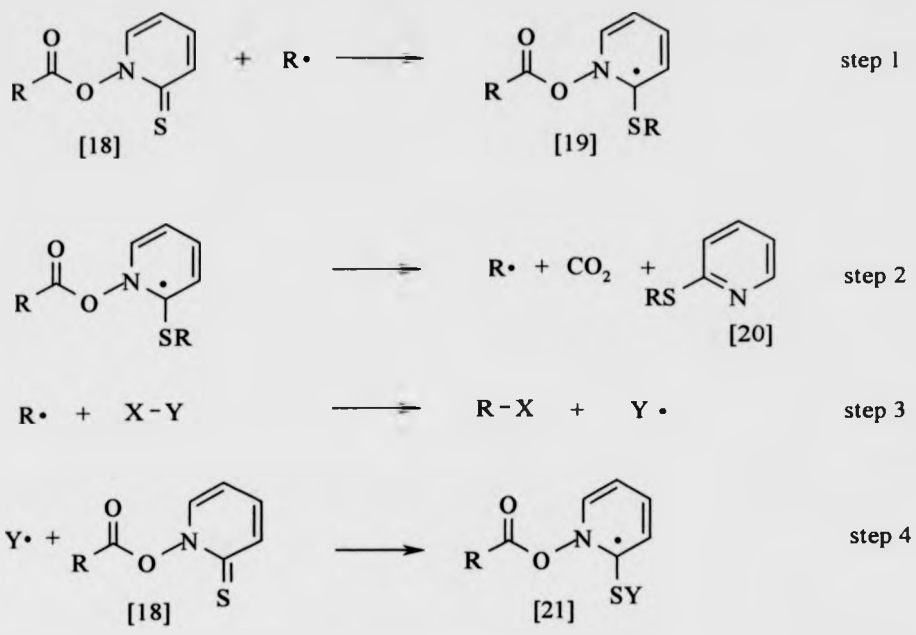


Scheme 1.15

In their most recently publication, they have reported the treatment of the polyene iodide [13] with TTMSS and AIBN in dry benzene *via* a syringe pump over 14 hours to give tricyclic ketone [16] and [17] (2:1, 65%).[18] The tricycles [16] and [17] are produced from [13] via 13-*endo*-trig radical macrocyclisation leading to the tridecadienone radical intermediate [14], followed by 6-*exo*-trig transannulation giving [15]. Competitive 5-*exo*-trig transannular cyclisations from [15] then produce the observed products [16] and [17] (Scheme 1.15).

1.3.2. The Thiohydroxamate Ester Method

This method has been developed by Barton and co-workers.[19] In this method, a chain-transfer agent is generated by using thiohydroxamic acid esters. The propagation sequence is showed in Scheme 1.16.



Scheme 1.16

Addition of the alkyl radical R· to thiohydroxamate [18] produces [19] (step1). Fragmentation of [19] (step 2) may be concerted or stepwise, involving an intermediate carboxyl radical. The alkyl radical (R·) is the chain carrying species. An enthalpic driving force for the reaction is provided by the formation of carbon dioxide and the aromatisation to the mercaptopyridine and an entropic driving force is provided by the formation of two molecules (CO_2 and [20]) from one ([18]). The alkyl radical must abstract an atom or group (X) from X-Y (step 3) or undergo an addition reaction at a rate more rapid than direct addition to the starting hydroxamate (step 1). The resulting radical Y· must add to the precursor (step 4) to produce [21], which then fragments according to step 2 to transfer the chain. The rate of step 4 much be rapid enough to maintain the chain. The relative rate of step 1 and 3 is extremely important

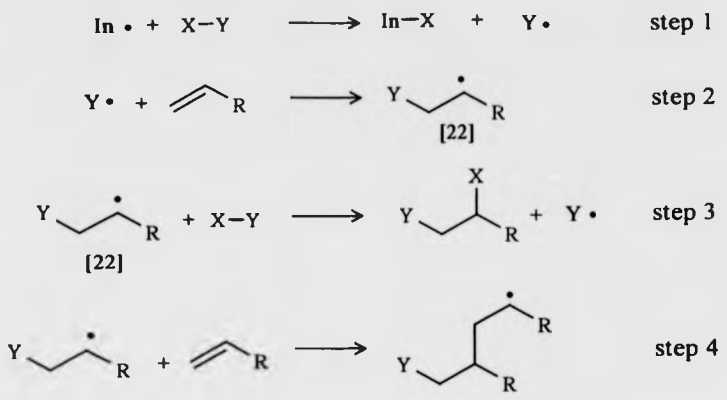
since these will ultimately control the rate of the alkyl radical. In the basic thiohydroxamate method, the lifetime of a radical is limited by the rate of addition to the starting thiohydroxamate (step 1).

1.4. Atom transfer radical method

In this process the final radical abstracts an atom from the starting material to furnish the observed final product and generate another starting radical. It is best illustrated by the transformation called the Kharasch reaction as shown in Scheme 1.17. In this reaction a reagent X-Y adds across a carbon-carbon double (or triple) bond. For an atom transfer chain to succeed, both the initial addition (or cyclisation) reaction and the atom transfer step must be relatively rapid and exothermic in order to compete with standard chain termination steps.

Scheme 1.17

A general mechanism for this addition reaction is shown in Scheme 1.18.[11]



Scheme 1.18

Initiation occurs by abstraction of X to provide the initial radical Y (step 1). Steps 2 and 3 constitute the propagation sequence. Addition of Y• to the alkene provides adduct [22]. The key chain transfer step 3 involves donation of an atom or group X from the starting material X-Y. The derived radical Y• is the chain transfer agent. In effect, both chain transfer and site selective generation of the initial radical are combined into this single step. Since the radical that undergoes addition (Y•) is generated directly by atom abstraction from the starting material X-Y, this class of reaction is called atom transfer addition.

For synthetic planning, it is wise to consider the elements that are required to provide a successful atom transfer chain. As with all radical chains, both propagation steps 2 and 3 must be relatively rapid, such that standard chain termination reactions cannot complete. An endothermic step is not tolerated, even if the other step is strongly exothermic. The best outcome results when both reactions are significantly exothermic.

To accelerate the atom transfer step 3, it is desirable to generate a radical Y· that is more stable (from a resonance energy standpoint) than the adduct radical [22]. On the other hand, increasing the resonance stabilisation of Y· relative to [22] reduces the exothermicity of the addition step 2. However, this step is already inherently favourable, because a π-bond is traded for a σ-bond. If the atom transfer step is slow then further addition of alkenes are possible leading to telomerisation (step 4).

1.4.1. Hydrogen Atom Transfer

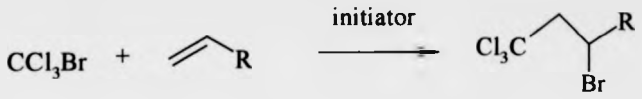
The hydrogen atom transfer approach leads to a reductively (H-atom) terminated reaction and lacks the major advantages of other atom transfer methods (such as halogen atom transfer) where the product generally retains useful functionality.[20] The method is generally only for the construction of simple molecules. Primarily, because only the most reactive C-H bonds will react fast enough to maintain a viable chain reaction. Consequently, the hydrogen-donor substrate is typically used in large excess in the absence of solvent and large amounts of initiator are also required.

1.4.2. Halogen Atom Transfer

The halogen atom transfer method is far more synthetically useful than the hydrogen atom transfer method for several reasons as follow.

- A versatile halogen atom is retained in the product.
- The atom transfer step is often very rapid, leading to an efficient chain process.
- Site specificity is seldom a problem because the carbon-(or heteroatom)- halogen bond is usually by far the weakest bond in the molecule.

Kharasch has investigated the addition of polyhaloalkanes across olefins.[21] A typical Kharasch reaction is shown below (Scheme 1.20).

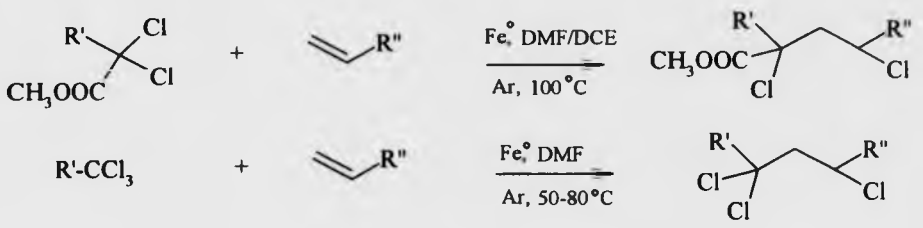


Scheme 1.20

In these processes, the initial and final radicals normally have very different solution lifetimes. The initial radical generally has a long lifetime because no reductant is present, and the final radical has a short lifetime because of the rapidity of halogen transfer.

Most recently, the use of alkyl trihaloacetates and dihalogenated esters have been used in halogen atom transfer addition reactions.[22,23] Forti and co-workers have recently shown that halogen atom transfer addition reactions of methyl 2,2-dichlorocarboxylates or trichloroacetic acid derivatives to alkenes can be efficiently

promoted by iron filings at 50 °C – 100 °C in N,N-dimethylformamide (DMF)/1,2-dichloroethane (DCE) (Scheme 1.21). [22]



Scheme 1.21

They also reported that the effect of temperature and solvent are important parameters for obtaining satisfactory results. At higher temperatures the reactions become faster but yields are reduced by the formation of telomeric by-products. The procedure is satisfactory only with terminal alkenes. Steric effects heavily hinder intermolecular radical addition when internal or cyclic alkenes are involved.[23]

1.4.3. The Transition Method-Promoted Free-Radical Reaction

In the last decade, the formation of a carbon-carbon bond using transition metal-promoted radical reactions has attracted great interest.[24] Transition metal-promoted radical reactions have found widespread use in organic synthesis. The development of this area is just realising its potential as evidenced from the application of this methodology at the retrosynthetic strategy-level during the synthesis of complex

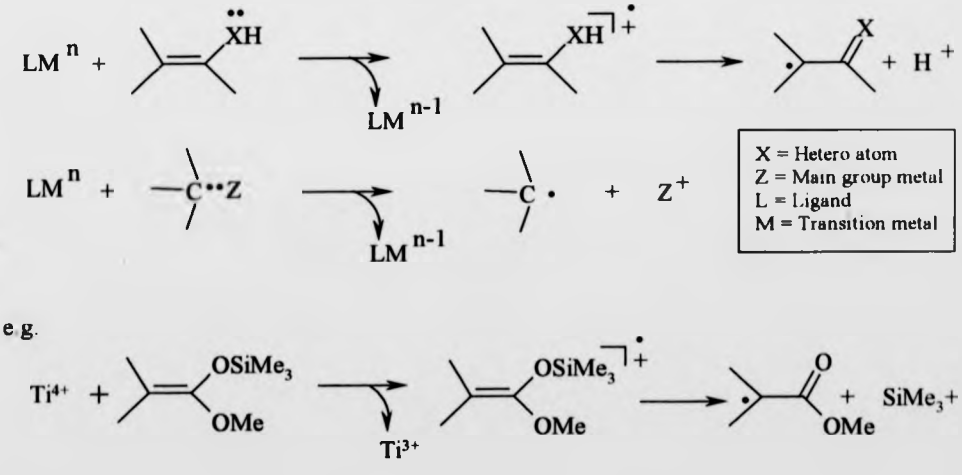
molecules. The most popular transition metal catalysts are based upon titanium, manganese, iron, cobalt, copper, and ruthenium complexes. Their reactions have emerged as important synthetic methods for new carbon-carbon bond formation. Transition metal-promoted reaction of carbon-centred radicals may be divided into the following two categories.

(I) Reaction of radicals generated by an oxidative process.

(II) Reaction of radicals generation by a reductive process.

(I) Oxidative Process.

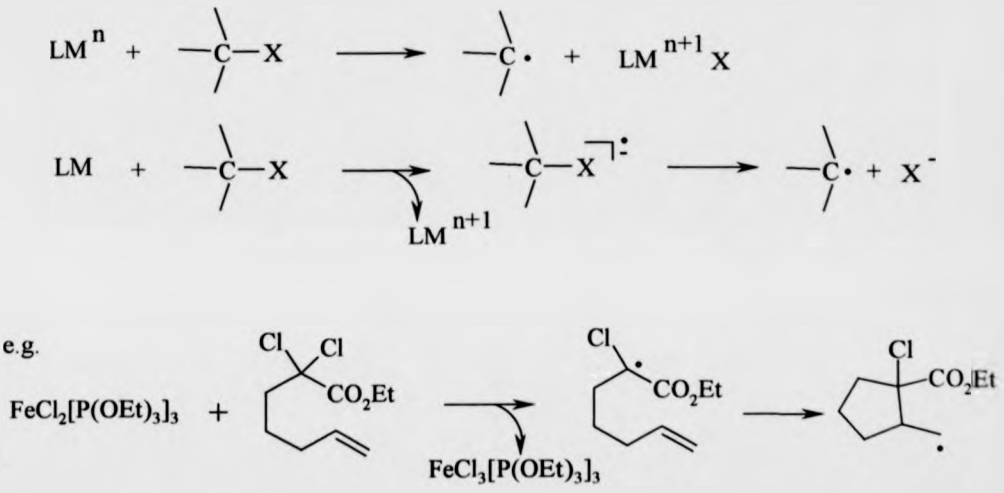
In this process, the metal acts as an oxidant and it involves the generation of radicals by an electron transfer from the radical precursor to the metal complex (Scheme 1.22). The reaction proceeds *via* an organometallic reagent which may lead to the carbon-centred radical on homolytic cleavage of carbon-metal bond.



Scheme 1.22

(II) Reductive Process

Alternatively, the metal can act as a reductant with the carbon-centred radical being generated by an atom transfer or electron transfer from the metal complex to the radical precursor. The reaction may proceed *via* an organometallic reagent which eventually leads to a free radical *via* homolytic cleavage of the metal-carbon bond (Scheme 1.24).



Scheme 1.24

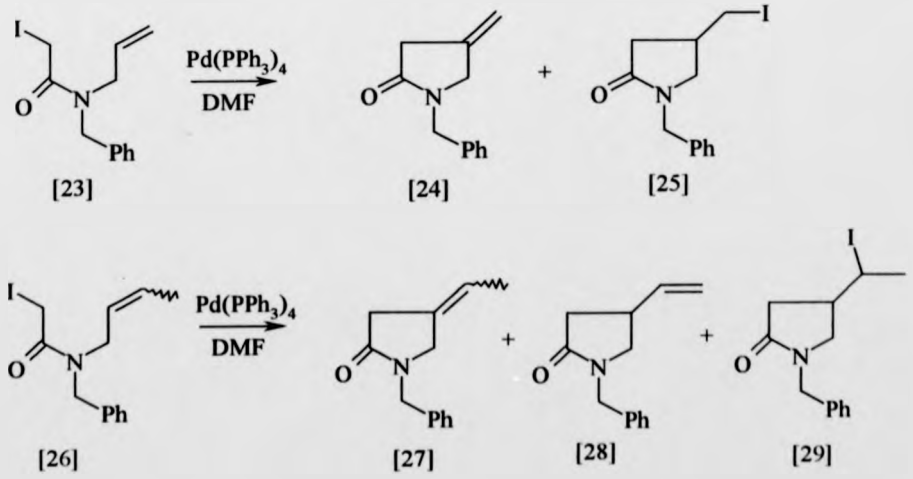
1.4.4. Halogen atom transfer cyclisation

The formation of rings *via* halogen atom transfer cyclisation has attracted recent interest. It has the advantage over conventional tin hydride mediated cyclisation

reactions in that the process is not reductive and leads to incorporation of functionality into the final products.

1.4.4.1. Palladium-catalysed cyclisation

In 1982, Ban and his group reported the cyclisation of N-allyl iodoacetamides using a palladium complex $Pd(PPh_3)_4$ as the catalyst of the reaction. [25] A key step was the intramolecular addition reaction of the carbon-iodine bone to an olefinic linkage. N-Benzyl-N-allyl-α-iodoacetamide [23] was warmed with an equimolar amount of $Pd(PPh_3)_4$ in dimethylformamide (DMF) at 65 °C for 5.5 hours to afford N-benzyl-3-methylene-2-pyrrolidone [24] and N-benzyl-3-iodomethyl-2-pyrrolidone [25] in a yield of 14% and 23% respectively. Compound [26] was also treated in the same manner to afford the desired cyclised products [27], [28] and [29] (Scheme 1.24).



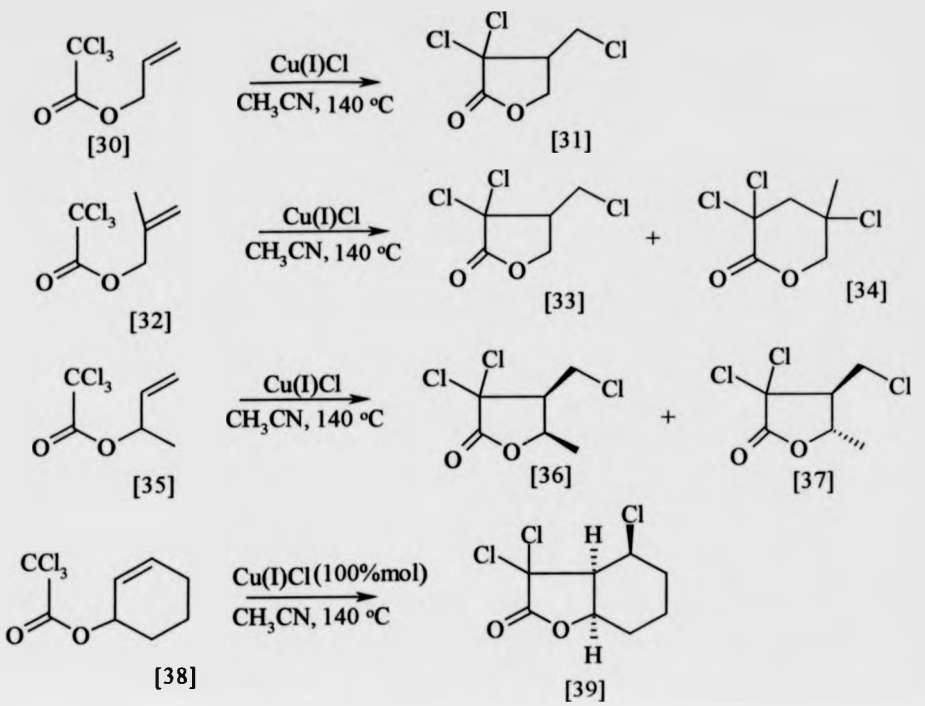
Scheme 1.24

The use of alternative solvents such as acetonitrile or toluene led to lower yields. If the reactions were carried out in the presence of bis(1,8-dimethylamino)-naphthalene (proton sponge) the cyclised products [25] and [29] were produced in greater yields (48% and 45% respectively). The main disadvantage with this approach was the relatively low yields of cyclised products.

1.4.4.2. Cyclisation of allyl trichloroacetates

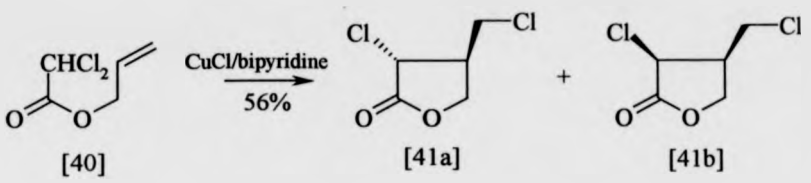
In 1983, Nagashima and co-workers reported that CuCl could mediate the cyclisation of allyl trichloroacetates [30].[26] The reactions were carried out in acetonitrile with a catalytic amount of Cu(I)Cl at 140 °C under argon atmosphere. The main products arose from 5-*exo* cyclisation as expected excepting the cyclisation of [32] which lead to competing amounts of 6-*endo* products due to steric hindrance by the methyl group at the 5-position of the alkene (Scheme 1.25).

In the reaction of the methyl substituted trichloroacetates [35], a high *cis*-selectivity was observed with ratio 9:1. The *cis*-selectivity was also apparent with the cyclic system [38], giving only the *cis*-fused isomer [39]. All the reactions required high temperature (e.g. sealed tube at 110 - 140 °C).



Scheme 1.25

They also found that the cyclisation was possible if CuCl was replaced with $RuCl_2(PPh_3)_3$, $RuCl(PPh_3)_3$ or $Cp_2Mo(CO)_6$.[27] However, large amounts of catalysts (10-30mol%) were required to attain high yields of the desired products. If the reactions were run at high concentration then telomerisation increased and low yields of cyclised products were obtained. The rate of the cyclisation of [30] in acetonitrile was found to be four times faster if a 1:1 mixture of Cu(I)Cl/bipyridine was used instead of just CuCl.

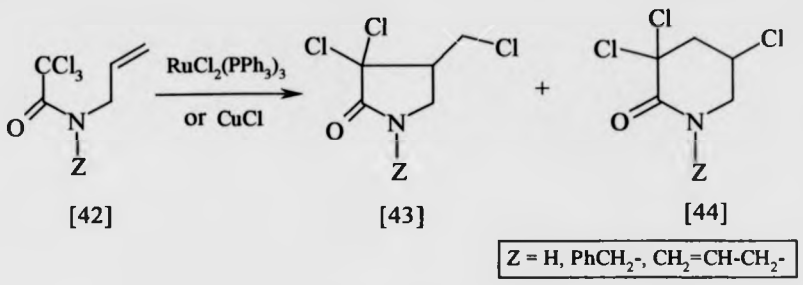


Scheme 1.26

Using this modified procedure it was possible to cyclise the less activated dichloride precursor [40]. This reaction was not possible using CuCl alone or if the ruthenium catalysts or organic peroxides were used.

1.4.4.3. Cyclisation of N-allyl trichloroacetamides

Very recently, the synthesis of γ-lactams *via* an analogous atom transfer cyclisation protocol has been examined.[28,29] Although the synthesis of γ-lactams *via* carbon-iodine bond formation using palladium-catalysed cyclisation has been reported by Ban and co-workers, its generally utility seems to be rather limited because of the low yields of the products. [25] The cyclisation of N-allyl trichloroacetamide [42] using CuCl or $RuCl_2(PPh_3)_3$ as a catalyst has been described by Nagashima and his group.[28,29] Using these procedures the corresponding γ-lactam [43] was obtained in high yield (Scheme 1.27). No completing δ-lactam [44] was detected.

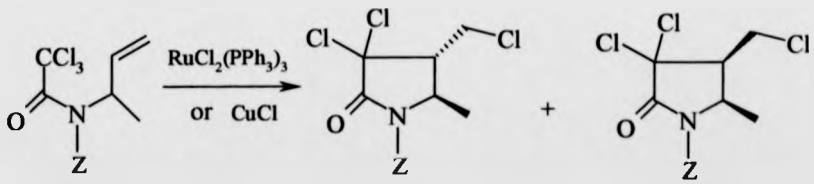


[42] [43] [44]

Z = H, $PhCH_2$-, CH_2=CH-CH_2-

Scheme 1.27

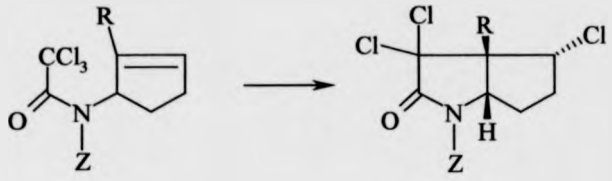
The stereochemistry of cyclisation of molecule [45] was found to be dependent upon the nitrogen protecting group, Z. For example, the cyclisation of 1-buten-3-yl trichloroacetamide [45] (Z=H) gave *trans*-β,-γ-dichloro-γ-lactam [46a] as a single product (Scheme 1.28) while its N-benzyl analogue (Z = CH_2Ph) gave a mixture of both the *trans* and *cis* lactams (*trans*:*cis* = 7: 3 at 80-140 °C). In contrast, with electron-withdrawing substituents on the nitrogen, (e.g. Ts, Ms, Cbz and t-BOC) the corresponding *cis* isomer was observed as the major product (*trans*:*cis* = 1:3 - 1:4 at 50-80 °C).[29]



[45] [46a] [46b]

Scheme 1.28

Itoh and co-workers reported that N-allyltrichloroacetamide [47] could be easily transformed into the corresponding trichlorinated γ-lactam [48] *via* either CuCl or $RuCl_2(PPh_3)_3$ catalysis (Scheme 1.29).[30,31]



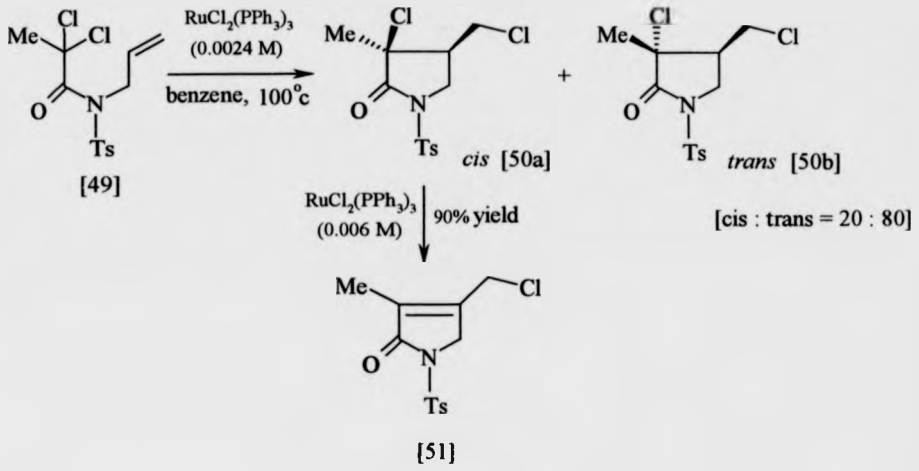
[47] [48]

Scheme 1.29

Although the use of CuCl and other atoms transfer procedures are simple and the products are generally isolated in high yields, the major disadvantage of these catalytic processes is that the reactions require high temperatures (>140 °C). Nagashima has developed alternative procedures which mediate cyclisations at lower temperatures.[32] The cyclisation of N-allyltrichloroacetamides can be achieved below room temperature by judicious choice of the catalyst and the protecting group on the amide nitrogen. The cyclisations of N-allyltrichloroacetamides with electron-withdrawing N-substituents such as Cbz or tosyl groups undergo reaction at room temperature or below using 30 mol% CuCl/bipyridine.

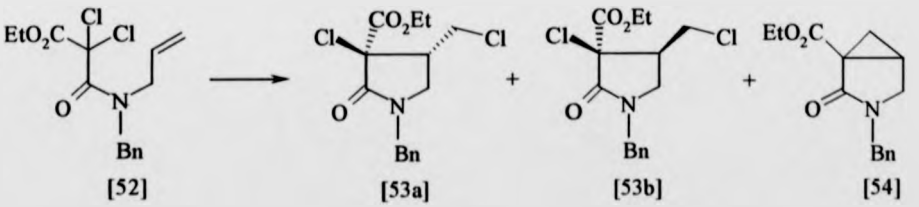
The effect of catalyst concentration was also found to be important in these reactions. With low concentration of catalyst (1%) considerable amounts of reduction products, e.g. N-allyldichloroacetamides were found as by-products.[33] In addition, during the study of using ruthenium mediated cyclisation of the N-tosyl amide [49], Slough

reported that higher concentrations could cause elimination of HCl from the initially formed product [50] giving rise to [51] (Scheme 1.30).[34]



Scheme 1.30

In another example, Bertrand reported that the treatment of dichloromalonamides with CuCl/bipy provided an easy access to fused five-three ring skeletons (Scheme 1.31).[35]

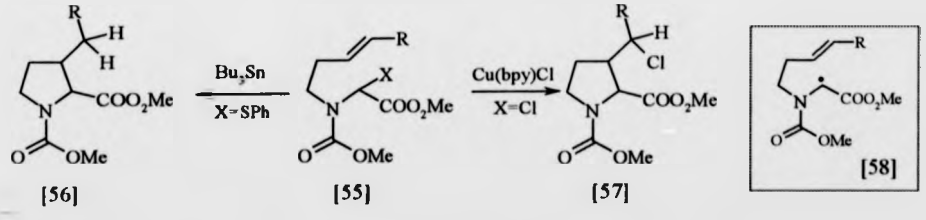


Scheme 1.31

In the presence of 0.1 equiv. of CuCl/bipy in isobutyronitrile at reflux for 16 hours, the two diastereomeric lactams [53a] and [53b] were isolated in 58% yield in a 6:4 ratio. When [52] was treated with 1 equivalent of catalyst, the ratio was reversed (4:6) and the bicyclic lactam [54] was also isolated (30%). If 2 equivalents of CuCl/bipy were used, lactam [54] was the only observed product (77% yield).

1.4.5. Comparison of the Cu(I)-catalysed cyclisation with Bu_3SnH-mediated cyclisations

Speckamp and Hiemstra [36] have reported that the copper(I)-catalysed cyclisation of α-chloroglycine derivatives [55] (X=Cl) to 3-(1-chloroalkyl)-substituted prolines [57] proceed with similar regio-and stereoselectivity to the Bu_3SnH mediated cyclisation of related α-(phenylthio)glycine (Scheme 1.32).



Scheme 1.32

The great similarities in regio-and stereoselectivity for both types of cyclisation suggest that the reactive intermediate in both reactions is the same (e.g. radical [58]).

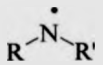
1.5. Nitrogen radicals

Although the application of carbon-centred radical reactions in synthesis has become increasingly popular, there has been less progress in the development of the reactions of hetero-atom centred radical systems. The potential for nitrogen radical mediated transformations is high, particularly in the fields of alkaloid and heterocyclic chemistry.[37]

The synthesis of nitrogen heterocycles by nitrogen radical cyclisation has been investigated by many groups,[38] most recently be Newcomb's[39] and Zard's[40] group. These researchers have developed methods for the synthesis of heterocycles under mild conditions which will allow access to a variety of natural product skeletons. This development is very important to the pharmaceutical industry which may use the developed methodology in the synthesis of new drug targets.

1.5.1. Aminyl radicals

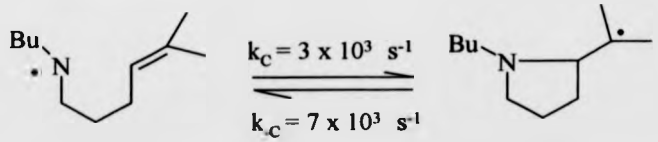
The neutral aminyl radical [59], also referred to as amino radicals, can be considered to be a nucleophilic species. They can be generated by decomposition of tetrazene precursors,[41] or oxidation of lithium amides.[42] Radicals generated by photolysis or thermolysis of a tetrazenes [43] do not undergo efficient radical chain reactions because high concentration of radicals are obtained and good propagation steps are not usually available.



[59]

Other precursors of aminyl radicals include N-chloroamines,[44] N-nitrosamines, [45] N-hydroxypyridine-2(1H)thione carbamates[46] and sulfenamides.[47]

The synthesis of nitrogen-heterocyclic molecules using radical chemistry has been primarily based on carbon-centred radical cyclisations using a nitrogen substituent in the chain.[48] In comparison, nitrogen radicals have not attracted the attention they deserve. One reason for the unpopularity of aminyl radicals in organic synthesis is the potential reversibility of the cyclisations with makes reactions synthetically useless. For example, the nucleophilic 4-pentenylaminyl radical [60] failed to cyclise in the reaction with Bu_3SnH because of an unfavourable equilibrium in favour of the uncyclised radical (Scheme 1.33).[49]

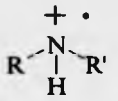


[60] [61]

Scheme 1.33

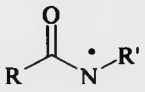
Consequently, other reaction pathways became available for aminyl radicals, for example, radical-radical couplings and disproportionation to amines and imines or reactions with solvent.[3]

A solution to these problems is to use an electrophilic radical, such as an aminium cation radical [62], a metal complexed aminyl radical [63] or an amidyl radical [64], all of which are electrophlic in nature.



[62]

[63]

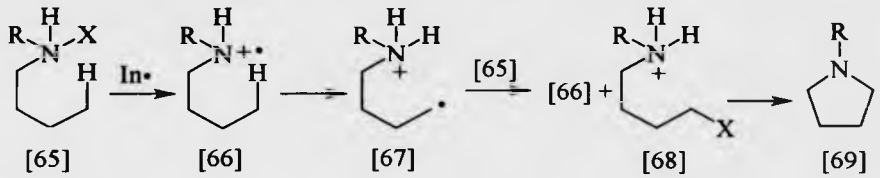


[64]

1.5.2. Aminium cation radicals and metal complexed aminyl radicals

Electrophilic nitrogen radicals can be generated by protonation of aminyl radicals with Bronsted acids or by complexation by Lewis acids.[50] Aminium cation radicals or metal complexed aminyl radicals show a remarkably different reactivity than do their electron rich aminyl radical progenitors. These radicals have been generated from N-chloroamines,[51] N-nitrosamines,[52] PTOC carbamates[53] and N-hydroxythiazide-2-thione carbamates.[54]

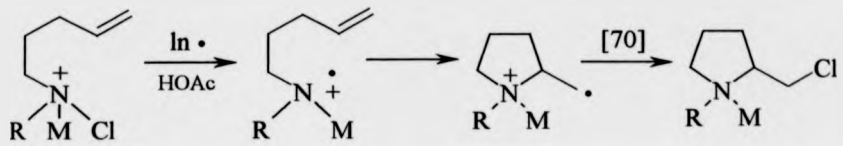
The Hofmann-Loffler-Freytag (HLF) reaction is a remote functionalisation reaction where an N-haloamine [65] is converted to a δ-haloamine [68] *via* the intermediate aminium cation radical [66]. Pyrrolidine products are obtained by cyclisation of the δ-haloamines under basic conditions [55] (Scheme 1.34). These radical chain reactions can be initiated by heat, UV photolysis, or metal ions.



[65] [66] [67] [68] [69]

Scheme 1.34

The chain reaction sequence for N-alkyl-N-chloro-4-pentenamine [70] involves as aminium cation radical ($M^+ = H^+$, Ti^{3+}, Fe^{2+}, or Cu^+)(Scheme 1.35).



[70]

Scheme 1.35

However, the use of an aminium cation radical or a metal complexed aminyl radical is limited in synthesis because the cyclisation takes place under acidic conditions.

1.5.3. Amidyl radicals

The chemistry of amidyl radicals has attracted much attention in the last three decades and has been reviewed.[56] These major interest has been how the electronic

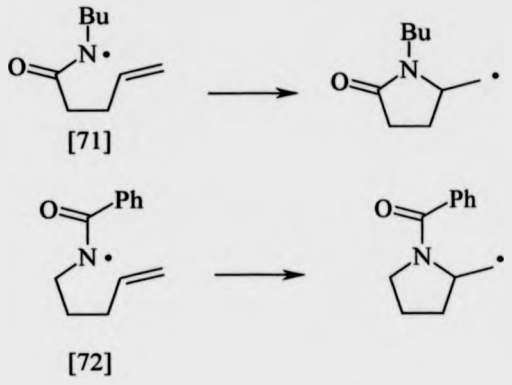
configuration of amidyl radicals effect their reaction with substrates and their reactivities.[57]

An amidyl radical [64] can be considered intermediate in reactivity between an aminyl or aminium cation radical due to the electron withdrawing ability of the carbonyl group. This allows efficient nitrogen-radical cyclisation to be conducted under strictly neutral conditions. The ability to work in neutral conditions is important when there are other acid-sensitive groups in the molecule.[37] By reduction of the resulting carbonyl group an amidyl radical cyclisation can become equivalent to the reaction of neutral dialkyl or monoalkyl aminyl radicals.

In intramolecular reactions onto double bonds, amidyl radicals selectively undergo *exo* cyclisation rather than *endo* cyclisation. [54] There are two modes of cyclisation of amidyl radicals. One is the cyclisation onto the acyl chain and another is the cyclisation onto the alkyl chain. Cyclisation of amidyl radicals is generally more favorable when the alkene is on the acyl side than on the alkyl side chain (Scheme 1.36).[58]

Scheme 1.36

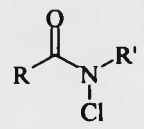
Newcomb and Esker have shown that 5-exo cyclisation of [71] is about 4 times faster than the corresponding 5-exo cyclisation of [72] (Scheme 1.37).

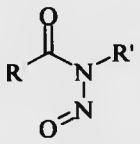


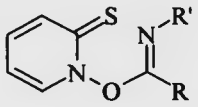
Scheme 1.37

1.5.4. Precursors for Amidyl radicals

Amidyl radicals have been generated from N-haloamides [73] and N-nitrosamides [74],[58] N-hydroxypyridine-2-thione imidate esters [75],[37] N-acyl-N-alkyl PTOC carbamate [76],[61] N-(phenylthio) amides [77],[62] O-benzoyl hydroxamic acid derivatives [78][63] and thiocarbazone derivatives [79].[64]


[73]


[74]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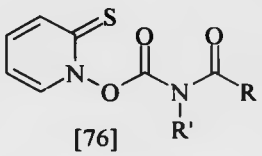
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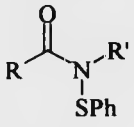
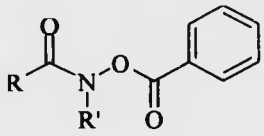

[77]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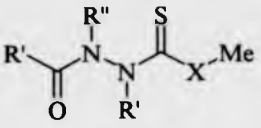
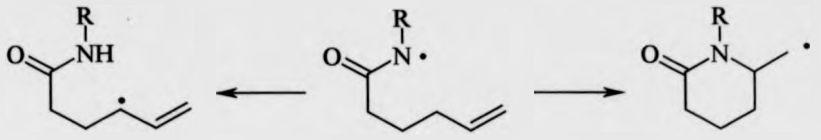

[79]

1.5.4.1. N-Halo and N-Nitrosoamides

Amidyl radicals derived from N-halo and N-nitrosoalkenylamides undergo efficient 5-exo cyclisation in neutral media to form substituted 2-pyrrolidinones and substituted pyrrolidine amides.

The cyclisation to form 6- membered rings by 6-exo cyclisation of an acyclic amide can be complicated by a competing 1,5-allylic hydrogen atom abstraction sequence that is promoted by the presence of halogen radicals that are formed on initiation (Scheme 1.38). Some efficient 6-exo cyclisations have been reported for cyclic amides and involve steric bias to hinder the abstraction pathway relative to cyclisation.[57]

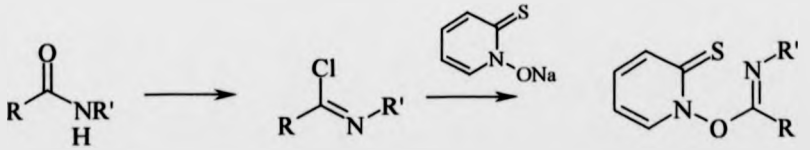


Scheme 1.38

Cyclisations of both these types precursors can be initiated by photodecomposition[59] of using benzoyl peroxide as initiator. [60]

1.5.4.2. N-Hydroxypyridine-2-thione imidate esters

Precursors of amidyl radicals can be produced by conversion of amides via the intermediate imidoyl chloride, into N-hydroxypyridine-2-thione imidate esters (PTOC imidate esters) [75] (Scheme 1.39).[37]

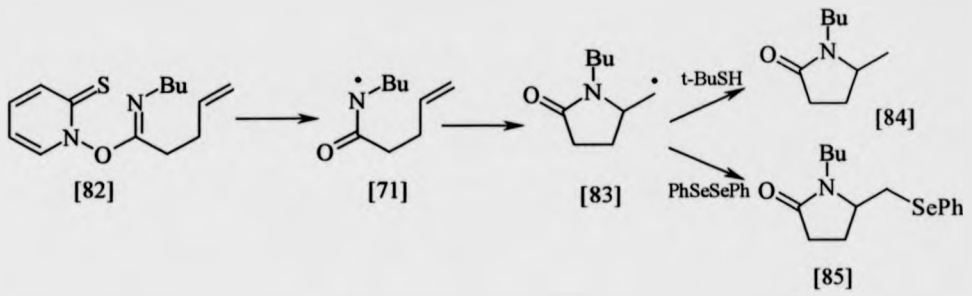


[80] [81] [75]

Scheme 1.39

The amidyl radical can be generated by reaction of the precursor in the presence of t-BuSH and visible light. For example, when precursor [82] and t-BuSH was irradiated with visible light, amidyl radical [71] was produced which underwent cyclisation in a

5-*exo* fashion to give the carbon-centred radical [83]. Subsequent reaction with the thiol gave [84] in a chain propagation step. A similar reaction run in the presence of Ph_2Se_2 gave lactam [85] (Scheme 1.40).

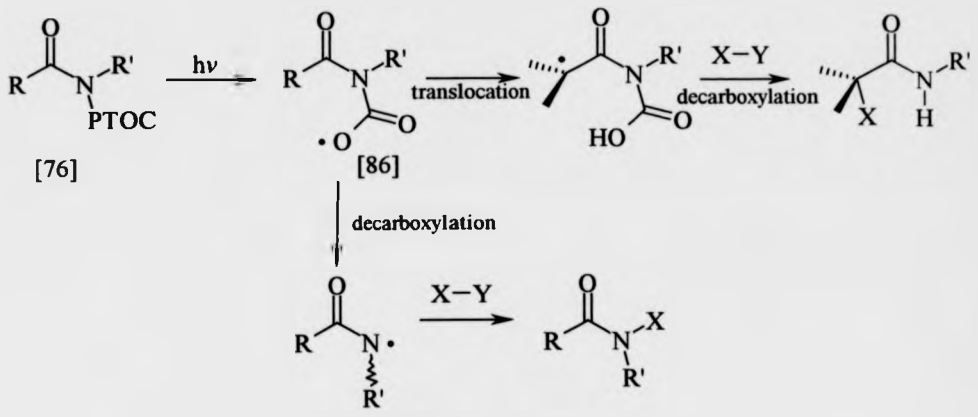


Scheme 1.40

Hence, N-alkylamidyl radicals are readily available from the imidate ester precursors [75][37] and intermediate cyclised radicals [83] *via* the precursor can undergo mild functionalisation. This protocol also avoids the problems associated with the strong reactivity of N-chloroamides which are active chlorinating agents.

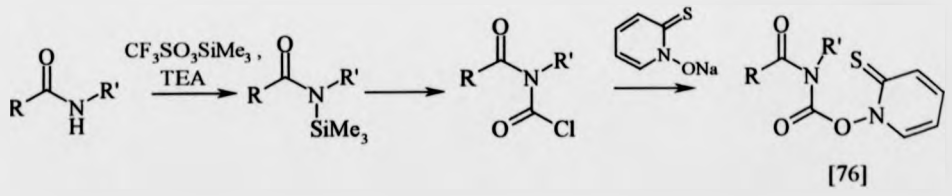
1.5.4.3. N-Acyl-N-alkyl PTOC carbamates

Another group of PTOC radical precursors, N-acyl-N-alkyl PTOC carbamates [76], are practical precursors for amidyl radicals. The precursors are readily prepared under mild conditions, although radical translocation of the produced radical [86] can be a problem but can be suppressed to a large extent by employing $MgBr_2$ in the reaction medium. This radical [86] can also undergo decarboxylation to furnish the desired amidyl radicals.[61] The reaction sequences shown in Scheme 1.41.



Scheme 1.41

The acyl PTOC carbamate precursors can be prepared in high yield from amide *via* the reaction sequence shown.



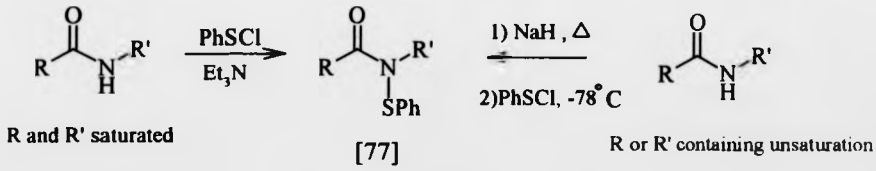
Scheme 1.42

Although these precursors are more stable than the PTOC imidate esters and of comparable stability to PTOC carbamates, they should be prepared immediately before use.

1.5.4.4. N-(phenylthio)amides

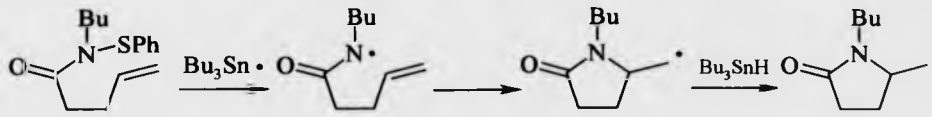
N-(phenylthio)amides [77] can be prepared in good to excellent yield from secondary amides. In radical-based synthesis applications where reduction of the final cyclised radical is desired, these precursors are good sources of amidyl radicals *via* tributyltin hydride mediated reactions. [62]

Simple N-(phenylthio)amides such as the derivative from N-methylacetamide (R=R'= CH_3) can be prepared in excellent yield by reaction of a secondary amide with phenylsulfenyl chloride and triethylamine. For alkenylamides in which electrophilic attack of the double bond by PhSCl was competitive, the amide was firstly deprotonated with NaH, and the resulting amide anion was allowed to reaction with PhSCl at –78 °C (Scheme 1.43).



Scheme 1.43

This method has been used to furnish precursors for intramolecular cyclisations, for example, the precursor [87] reacted in the presence of Bu_3SnH to initially give the amidyl radical [71] and then the lactam [84] in good yield (Scheme 1.44).

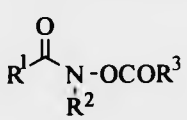


[87] [71] [84]

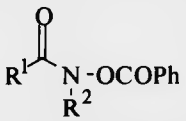
Scheme 1.44

1.5.4.5. O-Benzoyl hydroxamic acid derivatives

Zard recently discovered that amidyl radicals can be easily produced by the action of tributylstannane on O-acylhydroxamic acids [86].[63]



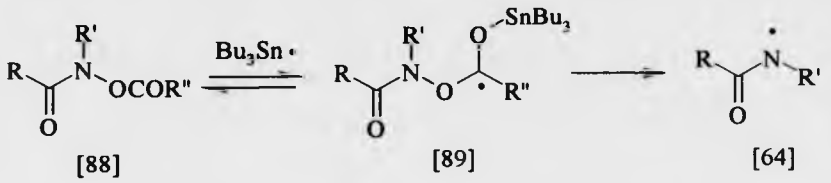
[88]



[78]

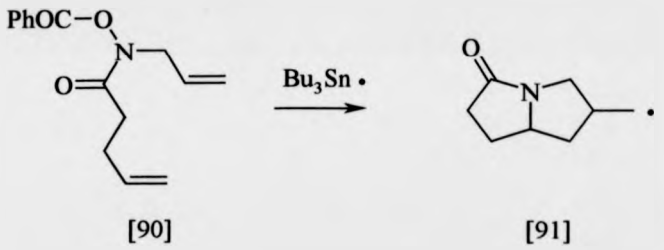
O-benzoyl hydroxamic acid

Zard has found that the esters of hydroxamic acid derivatives [88] are easily cleavaged with tributylstannane to generate the amidyl radicals *via* the intermediate of [89] (as shown in scheme 1.45). This is a mild and fairly general method for the generation of the required amidyl radicals. The first step in the sequence is reversible and thus by choosing R'' as Ph group the intermediate [89] can be stabilised thus biasing the equilibrium to this side and increasing the rate of the reaction.



Scheme 1.45

Amidyl radicals generated in this way can be easily incorporated into a number of cascade reaction sequences, for example, compound [90] gave bicyclic lactam [91] as a 2:1 mixture of epimers in 70% yield (Scheme 1.46).[63]



Scheme 1.46

1.5.4.6. Thiocarbazone derivatives

Thiocarbazone derivatives [79] are alternative precursors which can be used to generate nitrogen centred radicals including amidyl radicals. [64] The precursors are easily prepared by reacting the hydrazide [92] with the appropriate acid chloride (Scheme 1.47).

[92]

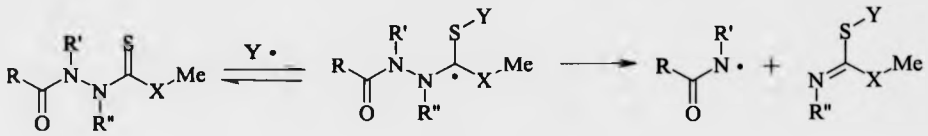
[X= O, S]

[79]

Thiocarbazone derivative

Scheme 1.47

These derivatives [79], contain a highly radicophilic thiocarbonyl group which upon addition to the radical $Y^{\bullet}$ create the intermediate [93] which is capable of undergoing β-scission to furnish the desired amidyl radical as summarised in Scheme 1.48.

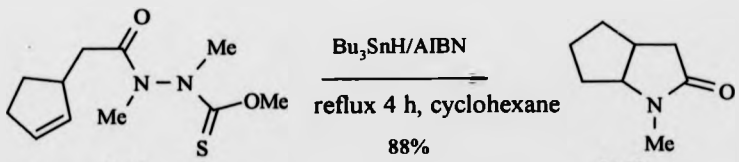


[79]

[93]

Scheme 1.48

For example, the lactam [95] was prepared in high yield (88%) from the precursor [94] by reaction with Bu_3SnH/AIBN (addition over 4 hours) in cyclohexane.



[94]

[95]

Scheme 1.49

CHAPTER 2

Investigations into the stereochemistry of amidyl radical cyclisations onto the alkyl side-chain

2.1. Introduction

In the recent years, the synthesis of heterocycles using amidyl radical cyclisation has been studied by several groups of investigators.[38,39,40] These investigations have demonstrated that nitrogen heterocyclic compounds can be prepared by mild and fairly general methods. However, the stereochemical outcomes of the cyclisations have been less well investigated.

For carbon radical cyclisation, Beckwith and Houk have developed the models for predicting the stereochemical outcome for substituted 5-hexenyl radicals.[65,66] The Beckwith model predicts that radicals cyclise *via* chair-like transition states.[65] The major product arises when the substituent occupies a pseudoequatorial position, while the minor product arises when the substituent is pseudoaxial (Figure 2.1). This rule was found to apply for substitution at C_2, C_3 or C_4. However, there was no discussion by Beckwith about substituent effects at C_1. Figure 2.1 shows the two transition states

for cyclisation of a C_3 methyl substituted 5-hexenyl radical. In general substitutents at C_1 lead to *cis* cyclised products.

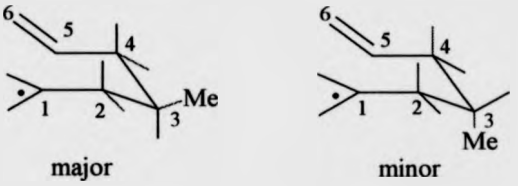


Figure 2.1 Chair-like transition state by Beckwith model

This model seriously over estimates the product ratio for C_2, C_3, or C_4 substitution but underestimates the *cis* preference for C_1 substitution. Houk has modified the model and predicts that minor products may arise from competing boat-like transition states[66] which have the substituents in pseudoequatorial positions (Figure 2.2).

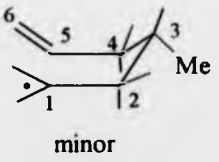
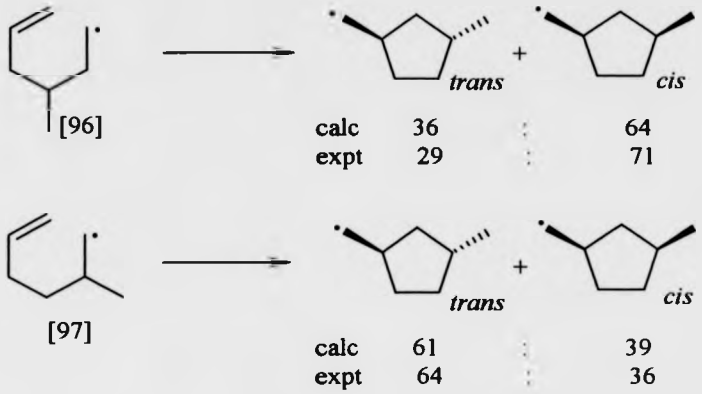


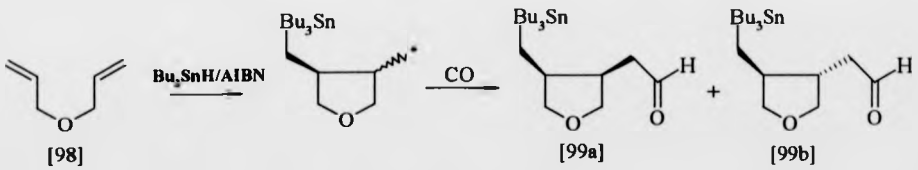
Figure 2.2 Boat-like transition state by Houk model

This transition state model predicts fairly accurately the outcome of cyclisation of the 3-methyl-5-hexenyl radical [96] and the 2-methyl-5-hexenyl radical [97] (Scheme 2.1).



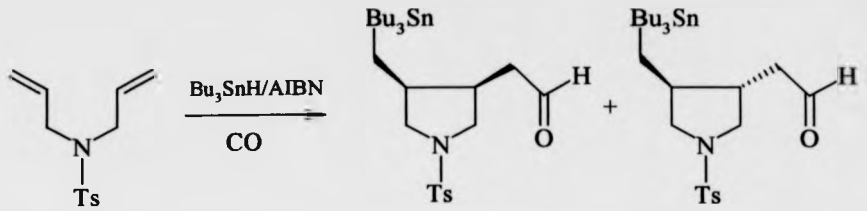
Scheme 2.1

Ryn and Sonada [67] have reported the cyclisations of 1,6-dienes which lead to the corresponding carbocyclic five membered rings. The stereochemistry of the cyclisations can be determined using the Beckwith and Houk models. In general, *cis* isomers were formed predominantly. The radicals were generated by treatment of 1,6-diallyl ether [98] with tin hydride and AIBN under CO pressure (Scheme 2.2)



Scheme 2.2

This cyclisation produced [99] in 59% yield with the ratio of *trans* to *cis* 39: 61. They also investigated the cyclisation of 1,2-diallyl amine [100] which gave 50% yield of [101a] and [101b] in the ratio 59:41 (Scheme 2.3).



[100] [101a] [101b]

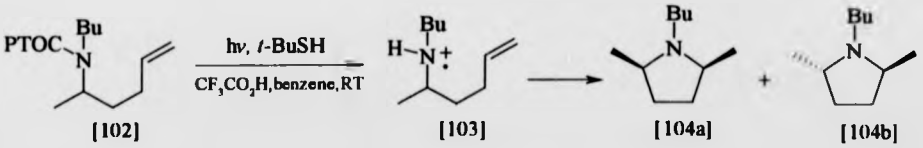
Scheme 2.3

These results agree with the Beckwith and Houk prediction for the 1-methyl-5-hexenyl radical cyclisation which cyclises to from a *cis* disubstituted cyclopentane preferentially (Scheme 2.4).

66 : 34

Scheme 2.4

For the cyclisations of nitrogen radicals, Newcomb has reported the stereochemical outcome of the cyclisation of N-butyl-2-methyl-4-penten-aminium cation radical [103] produced from PTOC carbamate [102] (Scheme 2.5).[68]



[102] [103] [104a] [104b]

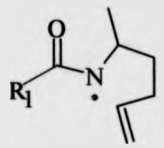
Scheme 2.5

The radical was generated by photolysis with a tungsten filament lamp at room temperature. In the presence of acid, pyrrolidines [104a] and [104b] were obtained in good yield (72%) by GC. The ratio of [104a] to [104b] was found to be 1:3. The preferential formation of the *trans* product [104b] is also predicted by the transition state models of Beckwith and Houk.

As mentioned earlier (Section 1.5.3), there are 2 modes of the amidyl radical cyclisation. Either the cyclisation can occur onto the acyl side-chain or onto the alkyl side-chain (Scheme 1.36). The Clark group has previously studied the stereochemical outcome of amidyl radical cyclisations onto the acyl side chain. [42e] Consequently only the cyclisations onto the alkyl side-chain are reported in this work. In particular, we investigated whether the effect of the nitrogen substituent R_1 could control the stereochemical outcome of the cyclisation (Scheme 2.6).

Scheme 2.6

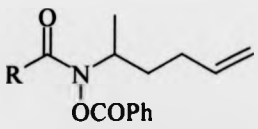
Initial work focused upon the cyclisation of amidyl radicals onto alkyl side chain with the R_2 substituent as a methyl group at the C_1 position.



[107]

2.2. Preparation of precursors

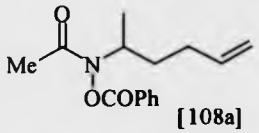
Although amidyl radicals can be generated from many precursors (Section 1.5.4), in this work, O-benzoyl hydroxamic acid derivatives were chosen as precursors for the radicals. Accordingly, we prepared a range of hydroxamic acid derivative of type [108].

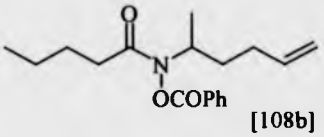


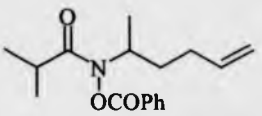
[108]

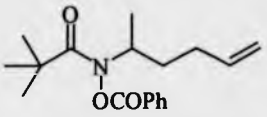
A number of R groups were chosen to determine how both steric and electronic effects would alter the outcome of the cyclisation reactions. Hence, the methyl group was chosen as a small primary R group [108a] while more bulky primary groups such as *n*-butyl [108b], benzyl [108f] and iso-butyl [108e] were also examined. Secondary and tertiary groups (iso-propyl [108c] and tert-butyl [108d]) were chosen to examine the

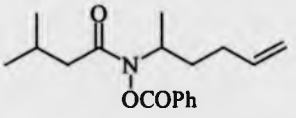
effect of bulk nearer the N-atom while electronic modification was also investigated, R= OMe [108g].

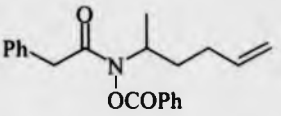

[108a]

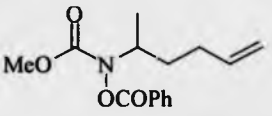

[108b]


[108c]


[108d]

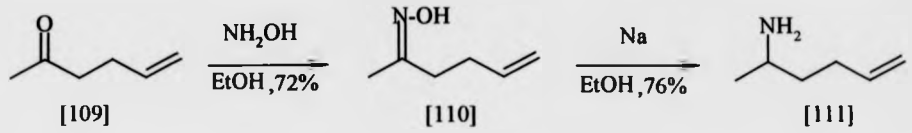

[108e]


[108f]


[108g]

The precursors were prepared by direct oxidation of 1-methyl pent-4-enylamine [111] with benzoyl peroxide followed by acylation with the appropriate acyl chloride (Scheme 2.8). Both of these steps were carried out in a one pot reactions based upon the procedure of Milewska.[69]

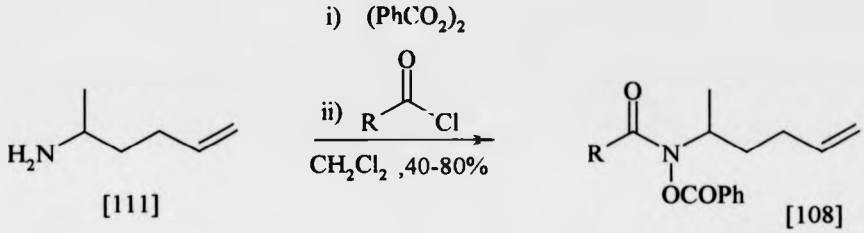
Hence, the amine [111] was initially required. This was prepared by the method of Venanzi.[70] First step, the ketone [109] was reacted with hydroxylamine hydrochloride to form oxime [110] which was then reduced with sodium in ethanol to give a desired amine [111] in 70% yield (Scheme 2.7).



[109] [110] [111]

Scheme 2.7

With amine [111] in hand each of the target precursors [108a]-[108g] were prepared as follows.



[111] [108]

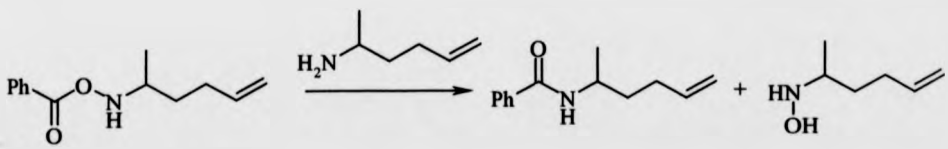
Scheme 2.8

Purification by column chromatography gave rise to the products [180a]-[108g] in the yields indicated in table 2.1.

Entry	Compound	R	Yield (%)
1	108a	**Me**	66
2	108b	**n-Bu**	51
3	108c	**i-Pr**	56
4	108d	**t-Bu**	39
5	108e	**i-Bu**	41
6	108f	**Bn**	35
7	108g	**OMe**	57

Table 2.1. The preparation of O-benzoyl hydroxamic acid derivatives

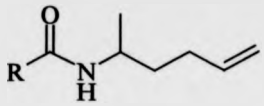
The yields of the precursors were between 35-60% with good yields being obtained when the R group was small (Me = 66%, OMe =57%). With larger R groups, lower yields were obtained (e.g. the *tert*-butyl group, 39%). In all cases substantial amounts of the by-product [113] were detected which also lowered the yields. This amide probably arises from the intermediate [112] by transfer of its acyl moiety *in situ* to the starting amine (Scheme 2.9).[70]



[112] [113]

Scheme 2.9

In most reactions, another by-product [114] was also obtained formed by competitive acylation of unreacted starting amine [111] with the appropriate acid chloride.



[114]

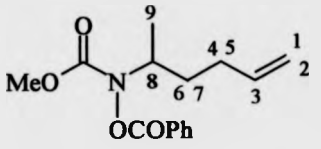
Interestingly, compound [108f] was obtained in the lowest yield (35%). For this reaction there was also a third by-product formed arising from the rearrangement of the O-benzoyl group from N to C-2 on the acyl side chain of the desired product (Scheme 2.10). The possible mechanism will be discussed later on in this chapter.

[108f] [115]

Scheme 2.10

Interestingly, the ^1H NMR of the hydroxamic acid derivatives [108a]-[108g] showed broad peaks in the 0-5ppm region of their spectra. For example, the ^1H NMR of compound [108g] shows very broad peaks at 4.67, 2.17, 1.74, 1.53 and 1.24 ppm. These were assigned as the peaks for the H_8, H_4 and H_5, H_6 and H_7, and H_9 respectively. The existence of the broad resonances suggested that there was restricted rotation around the C-N bond in this compound at room temperature. To test this theory a sample of [108g] was analysed by variable temperature NMR. Hence the spectrum of [108g] is shown at room temperature (Figure 2.3) and 50 ^oC (Figure 2.4). It can be seen that as the temperature rises the broad peaks sharpen as expected. Most

radical cyclisations are conducted at 80 °C or higher and consequently our compounds would be relatively conformationally mobile at this temperature.



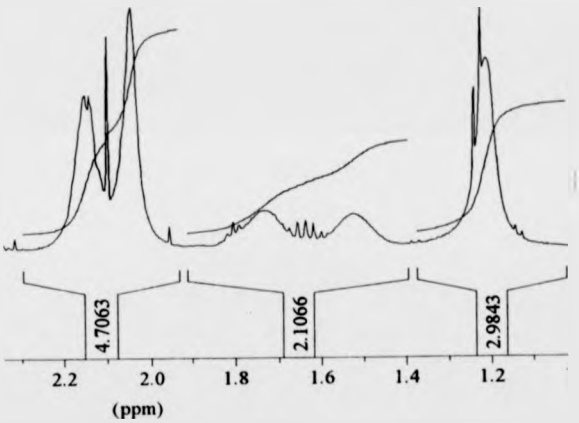


Figure 2.3. **^{1}H NMR spectrum of acetic acid benzoyloxy-1-methylpent-4-enyl amide [108g] at 298 K**

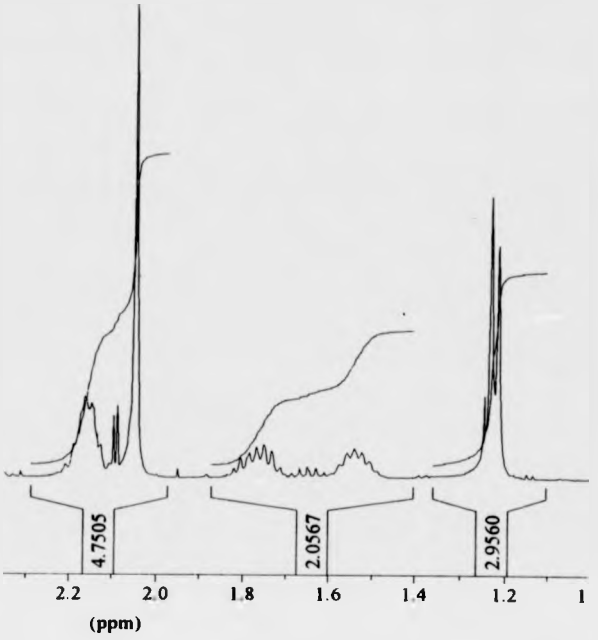


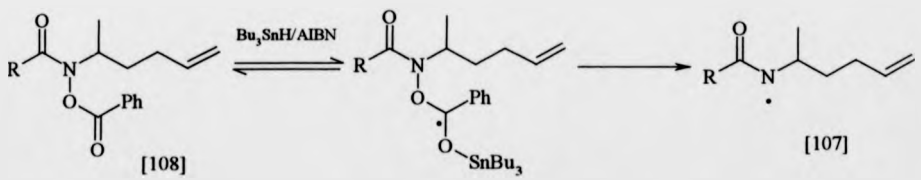
Figure 2.4. 1H NMR spectrum of acetic acid benzoyloxy-1-methylpent-4-enyl amide [108g] at 323 K

In the ^{13}C spectra of the precursors, [108a]-[108g], the peaks for both the carbonyl groups, COR and OCOPh, appeared very broad and with very low intensity. It was not uncommon to find that these peaks were so weak that they did not appear at all in the spectra even after spectra were re-run with long relaxation times with large quantities of sample. In addition, the peaks for the α-C in the alkyl chain attached to the N atom

(C-N) also appeared very broad and was sometimes absent. These phenomena are also likely to be due to restricted rotation of the C-N bond which has already been remarked in ^{1}H NMR spectra.

2.3. Cyclisation reactions

With the precursors [108a]-[108g] in hand, their cyclisations were then carried out using the tin hydride method of Zard.[63] Hence, the precursors were heated with tributyltin hydride and AIBN in refluxing toluene/cyclohexane to facilitate cleavage the weak N-O bond and to generate the amidyl radicals (Scheme 2.11).

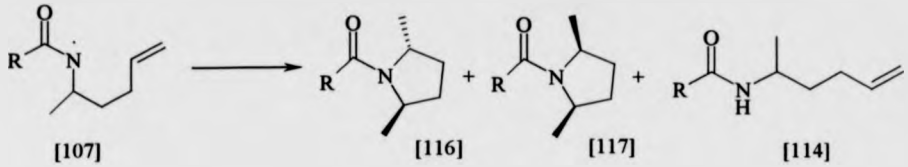


Scheme 2.11

All of the precursors were treated with tributyltin hydride (1.2 eq.) and AIBN (0.1 eq) in a degassed mixed solvent of toluene and cyclohexane. The initial concentration of substrate was 0.10 M. A syringe pump was used to deliver a low concentration of tin hydride over 6 hours. After addition, the mixtures were left to reflux for a further 12

hours. The reactions were monitored by TLC. In each cyclisation, if the TLC monitoring showed that there was still some starting material, an additional amount of tributyltin hydride (0.6 eq.) and AIBN (0.05 eq.) was added over another 6 hours. The reactions were then left to reflux for another 12 hours. After the reactions were complete the solvent was removed in vacuo and the residue partitioned between acetonitrile and hexane. ^{1}H NMR spectra showed that most of the tin residues and a little cyclised or reduced products were taken up in the hexane fraction. Consequently, the acetonitrile fraction was then further purified by column chromatography.

The result of the cyclisations are shown in table 2.2. The ratio of cyclised to reduced products and the ratio of diastereoisomers were determined from the crude NMR spectra of the residue from the acetonitrile fraction of the partition. The yields reported are the combined yields of both diastereoisomers and reduced products together as in most cases they could not be fully separated by column chromatography.



Entry	Radical	R	Yield (%)	red/cyclic	D.e. (%)
1	107a	**Me**	31[a]	1:5	54
2	107b	**n-Bu**	27[a]	1:10	56
3	107c	**i-Pr**	15[b]	-[e]	-
4	107d	**t-Bu**	-[c]	-[c]	-
5	107e	**i-Bu**	19[b]	-[e]	-
6	107f	**Bn**	16[a]	1:5	50
7	107g	**OMe**	13[d]	1:11	80

a combined yield of cyclised and reduced products
b yield of reduced product only
c no reaction, only starting material recovered
d yield of cyclised product only
e no cyclised product

Table 2.2 Cyclisations of N-benzoyloxy-1-methylpent-4-enylamides

The yields in table 2.2 are obviously low. This was a consequence of the difficulty in removing all the last traces of tin residues. Although the crude mass balances and NMR yields of the products were high, it was necessary to use repeated chromatography to remove all the last residues. The results above clearly indicate that the nature of the R group has an effect on the outcome of the cyclisations. When the R group was small or primary, both the desired cyclised compounds and the reduced products were detected (R=Me, *n*-Bu, Bn, OMe). For radicals [107c] and [107e] in which the R group size was increased to give more steric hindrance, only the reduced

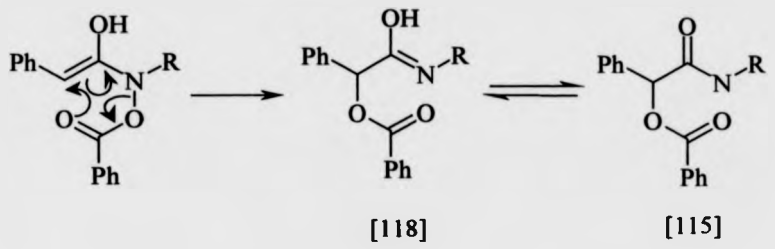
products were obtained in very low yields (15% and 19% respectively). In addition, when the R group was particularly hindered (e.g. R=*tert*-butyl) in radical [107d], only starting material was recovered even after the reaction was left for 4 days with 2 equivalents of Bu_3SnH. It is likely that compound [108d] did not undergo N-O homolysis to form the desired amidyl radical even under forcing condition primarily due to the increased steric hindrance at nitrogen which inhibits the initial reversible attack of the Bu_3Sn radical onto the adjacent carbonyl oxygen atom.

When the R group was changed from Me to *n*-Bu and to Bn, there was a little effect on the diastereoselectivities of the reactions (54, 56 and 50 % diastereomer excess respectively). More interesting however was the apparent increase in diastereoselectivity for the cyclisation of compound [108g] (80% d.e.). The precise reason for this behaviour is uncertain although it is likely to be electronic in origin. The electronic nature of the radical (a carbamyl radical) makes it more nucleophilic than the corresponding amidyl radicals. This may explain its apparent greater rate of cyclisation, but how it effects the selectivity of cyclisation is unknown.

The cyclisation of the benzyl derived precursor [108f] deserves same comment. As well as the cyclised compounds [116f] and [117f] a significant amount of the rearranged amide [115] was detected (40%). This was also isolated during the synthesis of this substrate (see section 2.2).

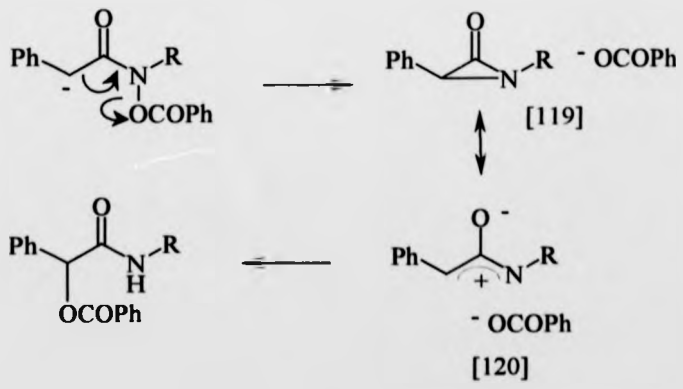
There are 2 possible mechanisms which could explain the formation of the rearrangement compound [115].

First, is a novel [3,3] sigmatropic rearrangement from the enol [118] as shown in Scheme 2.12.[71]



Scheme 2.12

Second, is an intermolecular 1,3-elimination of the O-acyl leaving group furnishing an α-lactam [119] which undergoes ring opening to the ion pair intermediate [120] which is subsequently trapped by the liberated benzoates anion. This mechanism is similar to that hypothesised for the conversion of O-sulfonylated N-alkyl hydroxamic acids to 2-substituted N-alkyl amides reported by Hoffman (Scheme 2.13). [72]

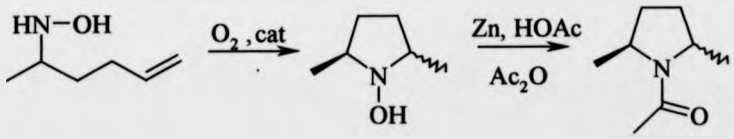


Scheme 2.13

2.4. Confirmation of the structures of cyclised products

The ratio of diastereomers formed in each cyclisation was determined by integration of their 400 MHz ^1H spectra. The major diastereomers were identified to be *trans* by comparison of their spectral details with authentic samples prepared unambiguously.

N-Acetyl-2,5-dimethylpyrrolidine [123] has been previously produced by cyclisation of hydroxylamine [121]. Subsequent reduction and acetylation with Zn, HOAc, and Ac_2O afforded the 1-methylpent-4-enylamine [123] (Scheme 2.14). [73]

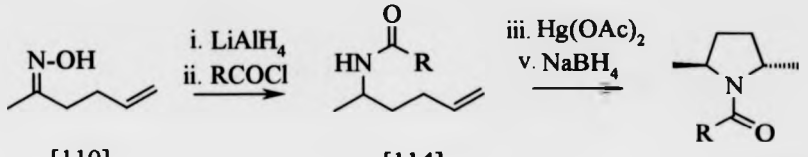


[121] [122] [123]

Scheme 2.14

NMR analysis showed that the final amide [123] was a mixture of stereoisomers; 35% *cis* isomer and 65% *trans* isomer. An alternative cyclisation method towards this compound has been reported by Harding and Burfs.[74] They were interested in the stereoselectivity of the electrophile-initiated cyclisation of δ-alkenyl amide derivative

[114]. They report that N-acetyl-*trans*-2,5-dimethylpyrrolidine [116a] and N-carbomethoxy-*trans*-2,5-dimethylpyrrolidine [116g] were produced almost exclusively by an intramolecular amidomercuration of [114a] and [114g] (R = Me, OMe). They reported that reduction of the oxime [110] with lithium aluminium hydride and direct acetylation of the crude product gave the amide [114] in 80-90% yield. Treatment with mercuric acetate in tetrahydrofuran followed by reduction with sodium borohydride gave the cyclisation product [116], in 90-98 % yield (Scheme 2.15). Harding has reported that the proportion of *cis* isomer is estimated to be approximately 2% by comparison with a sample containing added *cis* isomer.

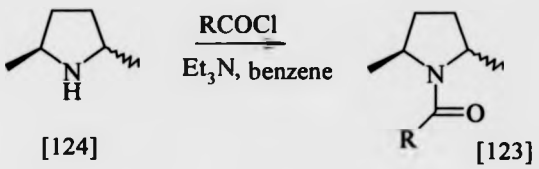


[110] [114] [116]

Scheme 2.15

We therefore subjected the oxime [110] prepared previously to this intramolecular amidomercuration in order to prepare an authentic sample of the *trans* isomer of [116a] to compare it with the pyrrolidines formed by our amidyl radical cyclisation. From this comparison, we concluded that the major diastereomer formed from the amidyl radical cyclisation of [108a] was the *trans* pyrrolidine.

In order to confirm the structure of the major cyclised compound formed from the cyclisation of radicals [107b], [107f] and [107g] and due to the difficulty of preparing compounds [116b], [116f] and [116g] by the amido mercuration procedure. Authentic samples were prepared by acylation of a 2:1 mixture of the *cis* and *trans* isomers of commercially available 2,5-dimethylpyrrolidine [124] (from Aldrich) as shown in Scheme 2.16. [73]



[124] [123]

Scheme 2.16

The major products from the amidyl radical cyclisations of compounds [108b] and [108f] were assigned as a *trans* based upon comparison of the carbon shifts of the methyl groups with the authentic samples prepared. The carbon methyl shifts of the *cis* isomers generally appear further downfield than those of the *trans* isomers.

2.5 Explanation for the formation of cyclised products

The major isomers of the cyclisations were shown to be the *trans* isomers. The stereoselectivity matches that predicted by the Beckwith model. This can be explained by invoking 'chair like' transition states for the cyclisations. The major transition states contain the methyl group in a pseudo equatorial position (a and c), predicted to be of lower energy by Beckwith. These lead to the major *trans* product [116]. The minor transition states (b and d), lead to the minor *cis* product [117] and have the methyl substituent in the axial orientation and are consequently less favoured. It is assumed that no contributions due to the higher energy boat transition states occur. Therefore, there are four possible 'chair like' transition states in the cyclisations (Figure 2.6).

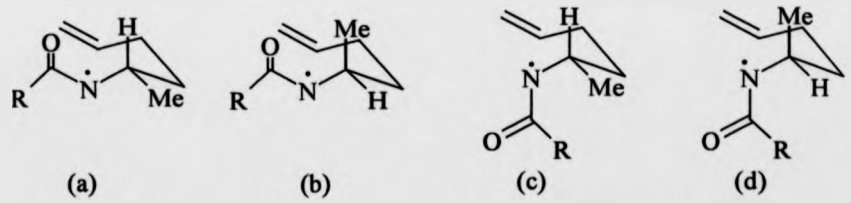
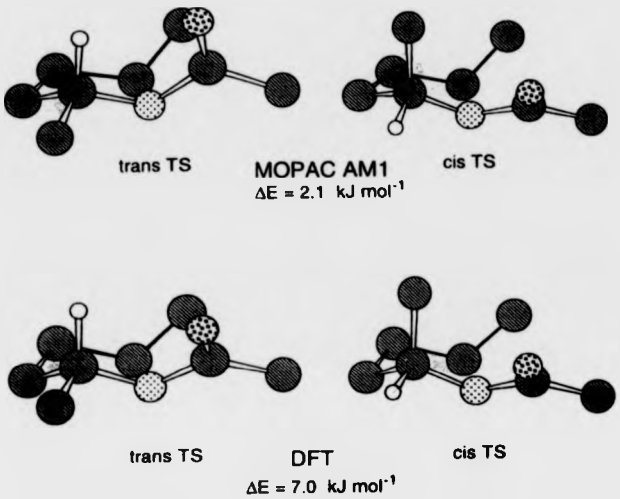


Figure 2.5. The possible 'chair-like' transition states

Moreover, semi-empirical molecular-orbital (MO) calculations using the AM1 [75] approximation, as implemented in version 6 of MOPAC [76] indicated that the transition state for cyclisation of [107a] to [116a] was lower in energy than that to [117a] (ΔE =

2.1 kJ mol^{-1}). In addition the higher level ab initio calculations, Density Funtional Theory Calculations (DFT),[77] which were performed using the Amsterdam Density Functional Program version 2.3[78] also indicated that the transition state for cyclisation of [107a] to [116a] was lower in energy (ΔE = 7.0 kJ mol^{-1}).



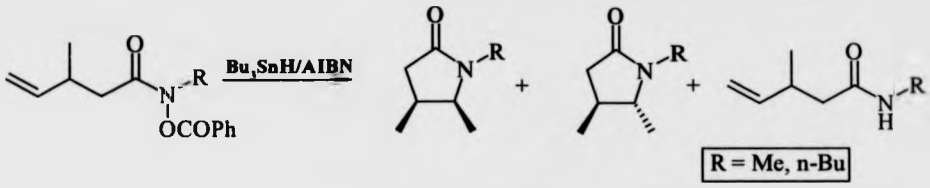
2.6. Conclusion

In this chapter, the effect of the nitrogen substituent upon the stereoselectivity of the amidyl radical cyclisations was investigated. The results from the experiments indicated that the *trans* isomers were the major isomers of the cyclised products. The *trans* stereoselectivity matches that predicted by Beckwith for the C-radical cyclisations.

Therefore, it can be assumed that the radicals cyclise *via* a 'chair-like' transition state with the methyl group in an equatorial position. This could be confirmed by MO calculations (AM1 and DFT) that showed that the transition state for cyclisation of [107a] to the *trans* isomer cyclised product [116a] was lower in energy than that to the corresponding *cis* isomer cyclised product [117a]. The greatest diastereoselectivity was established when the nitrogen substituent was a methoxycarbonyl group. It was assumed that the electronic nature of the nitrogen may affect the stereoselectivity although how this electronic effect influences the stereoselectivity is less certain. This electronic nature, however, was found to increase the rate of the cyclisation presumably due to the greater nucleophilicity of the radical. For the cyclisations with primary alkyl substituents, the diastereoselectivities of the reactions were similar. However, the cyclisation afforded low yields of desired cyclised products due to the difficulty in removing the tin-residues.

Interestingly, the diastereoselectivity of the reactions are significantly better than for the cyclisation of the 2-methyl-5-hexenyl carbon radical [97] (30% de) and for the related amidyl radical cyclisations proceeding in the acyl mode (10-17% de). Comparing these results with those recently obtained [79] for the cyclisation of amidyl radical in the acyl mode (Scheme 2.17) we can see certain similarities. These results also showed a preference for the *trans* cyclised product, however the diastereoselectivities were significantly lower (10-17% d.e.) due to there being less energy difference between pseudo equatorial and axial positions in the transition states. However, the yields of the cyclisation products were better (47-55%) due to the greater rate of the cyclisations. Hence, amidyl radical cyclisations onto the acyl side-

chain of substrates (Scheme 2.17) is more favoured than the cyclisation carried onto the alkyl side-chain of substrates [108], however the selectivity is much poorer.[58]



Scheme 2.17

CHAPTER 3

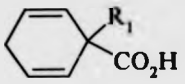
Non-tin hydride method of amidyl radical cyclisations

3.1. Introduction

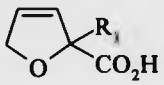
The synthetic applications of the amidyl radical cyclisations investigated in the last chapter were somewhat limited by the difficulty of removing the tin-residues and by the high toxicity of the Bu_3SnH reagent. We consequently searched for alternative methods to generate our amidyl radicals.

Due to the relative ease of forming the N-alkyl-O-acyl hydroxamic acid precursors, we wished to continue to use these substrates in our efforts to find new ways of producing amidyl radicals.

The radical chain decompositions of esters of cyclohexa-1,4-diene-3-carboxylic acids [125] and 2,5-dihydrofuran-2-carboxylic acid [126] to give carbon-centred radical have been published by Walton and co-workers in 1995.[80]

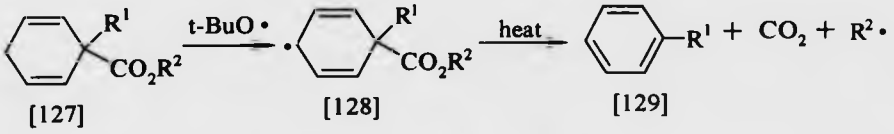


[125]

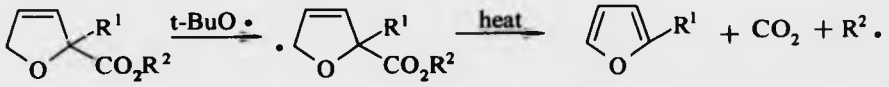


[126]

The esters of both molecules contain allylic or bisallylic hydrogens which will be readily abstracted by initiator radicals. Therefore an intermediate cyclohexadienyl [128] or dihydrofuranyl radical [131] will be formed with high selectivity (Scheme 3.1)



[127] [128] [129]

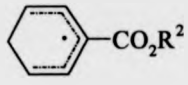


[130] [131] [132]

Scheme 3.1

Formation of the aromatic product [129] or [132] provides the driving force for decarboxylation. The alkyl radical R^2 produced in this step can then take part in intra- or inter-molecular reactions before continuing the chain by reacting with another molecule of [127] or [130]. The attractive feature of this scheme is that in each case the aromatic by-product, [129] or [132], is easily removed because of its volatility.

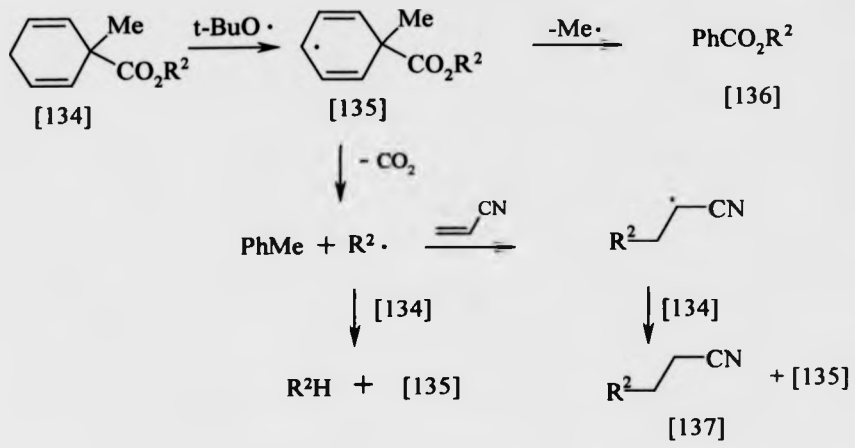
Intermolecular reaction of the released alkyl radical (R^2 radical) with halogen donors (N-bromosuccinimide, NBS) was initially investigated by Walton. When R^1 was H, it was found that the reaction afforded the alkyl bromide in a low yield and that additional side products were also formed, primarily because loss of the hydrogen (R^1) radical from the ester [127] took place forming the cyclohexadienyl radical [133]. This radical [133] could not decarboxylate and hence the reaction became complex and low yielding. When R^1 was a methyl group, analogous loss of the methyl radical from ester [127] was more difficult.



[133]

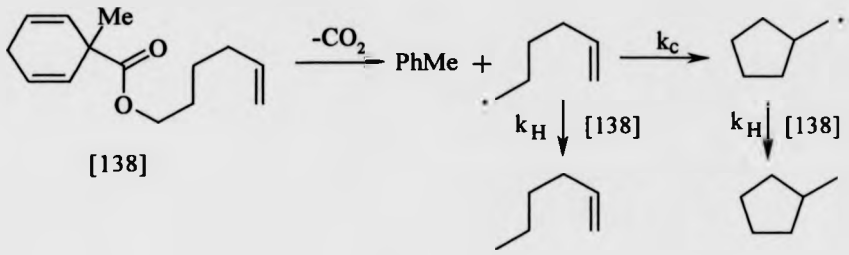
Subsequently, Walton studied the intermolecular chain additions of radical R^2 with acrylonitrile. The radical [135] was generated by thermal initiation at 140 °C with di-*tert*-butylperoxide in *tert*-butyl benzene or benzene solution in sealed tube. The reaction gave the expected adducted [137] together with reduced product (RH) and significant amounts of benzyl ester [136] (Scheme 3.2).

The comparable amount of R^2H formed showed that the alkyl R^2 radical readily abstracts a hydrogen atom from [134] almost as readily as its addition to acrylonitrile. The significant yield of benzoic acid ester [136] showed that methyl radical loss was significant at this high temperature.



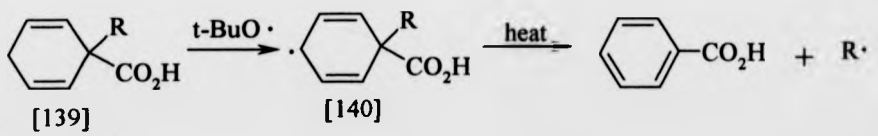
Scheme 3.2

In order to investigate intramolecular cyclisation, the hex-5-enyl ester [138] was prepared as a radical precursor. The ester [138] was decomposed at 140 °C in *tert*-butyl benzene solution to give toluene and the cyclised product, methylcyclopentane together with reduced product, hex-1-ene. It was found that the minor amounts of cyclohexane and hex-5-enyl-benzoate were formed as by-products (Scheme 3.3). The ratio of the rate constants for cyclisation (k_c) to hydrogen abstraction from [138] (k_H) was also determined to be: $k_H/k_c = 1.3 \times 10^{-2}$ dm^{-3} mol^{-1}s^{-1}.



Scheme 3.3

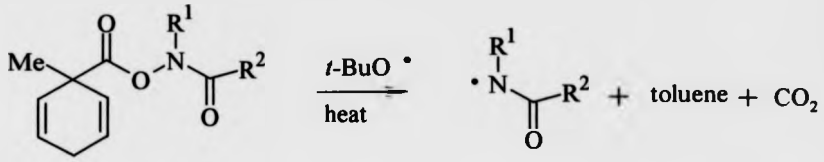
The study of the rate of hydrogen abstraction by alkyl radicals from cyclohexa-1,4-dienyl esters indicated that they were slower hydrogen donors than organotin hydrides. Furthermore, Walton also reported that cyclohexadienyl radicals [140] generated by hydrogen abstraction from several different 3-alkylcyclohexa-1,3-diene-3-carboxylic acids [139] gave the corresponding carbon-centred radicals (R•). The C-C bond is homolytically cleaved with the driving force being formation of the aromatic benzoic acid (Scheme 3.4). [81]



Scheme 3.4

These alkyl radicals (R•) so generated could undergo either inter- or intra-chain addition reactions with alkenes to afforded adduct compounds. Alkyl halides could also be produced by trapping the intermediate radicals (R•) with halogen donors.

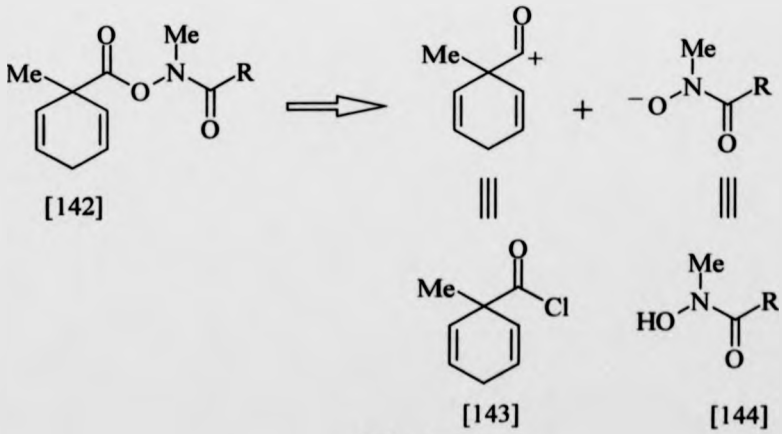
This work prompted us to investigate whether the amidyl radicals could be generated from appropriate precursors [141] using this approach (Scheme 3.5).



[141]

3.2. Preparation of radical precursors

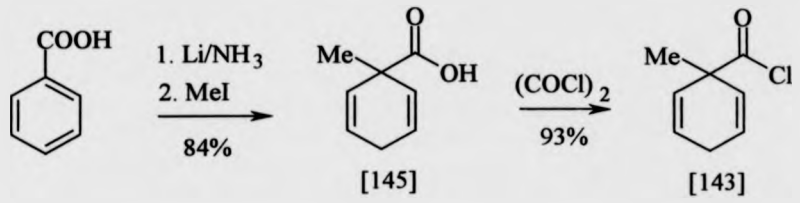
Our first attempt was the preparation of the precursor [141] with R^1 = Me and R^2 = Ph or $CH_2CH_2CH{=}CH_2$. In order to prepare these new carboxylate precursors [142], the carboxyl chloride [143] and the hydroxamic acids [144] were needed as shown by the retrosynthetic analysis in Scheme 3.6.



[142] [143] [144]

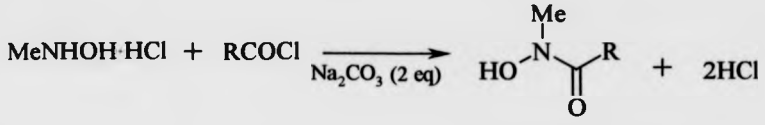
Scheme 3.6

The carboxylic acid [145] was readily accessed by Birch reduction of benzoic acid followed by quenching the lithium/ammonia solution with an iodomethane.[82] The acid [145] was then reacted with oxalyl chloride to afford the carboxyl chloride [143] (Scheme 3.7).



Scheme 3.7

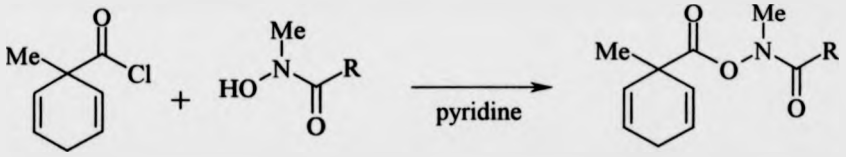
The first step of this sequence provided the desired product [145] in 84% yield with a very small amount of 1,5-cyclohexadiene-1-carboxylic acid obtained as a by-product. The other partners required for the synthesis of the amidyl radical precursors [142] were the hydroxamic acids [144a] and [144b] prepared by the reaction of methyl hydroxylamine hydrochloride with the appropriate acid chloride in the presence of two equivalents of Na_2CO_3 (Scheme 3.8). The benzoyl group was chosen as a simple N-substituent in order to assess whether the chemistry could be accomplished. While the penten-4-oyl group in [144b] was chosen to present the correct alkene chain on which the N-substituent of the amidyl radical released from the reaction was supposed to undergo cyclisation to give a cyclised product. The penten-4-oyl chloride was prepared by refluxing penten-4-oic acid with oxalyl chloride for 1 hour.



[144] a : R = Ph
b : R = $CH_2CH_2CH{=}CH_2$

Scheme 3.8

Both compounds [144a] and [144b] were produced in good yield (50% and 70% respectively). With the cyclohexadiene carboxyl chloride [143] and the hydroxylamides [144a] and [144b] in hand, the carboxylate precursors [142a] and [142b] were then prepared. Both reactions were carried out in dichloromethane solution at room temperature in the presence of 1 equivalent pyridine (Scheme 3.9).



[143] [144] [142]

a : R = Ph
b : R = $CH_2CH_2CH{=}CH_2$

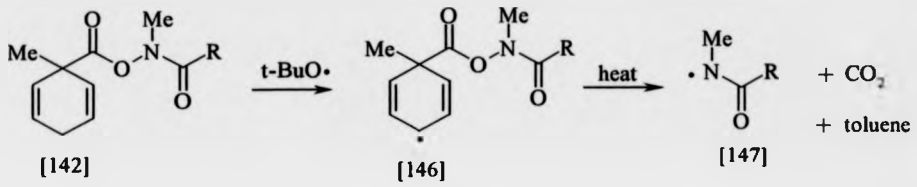
Scheme 3.9

Both reactions were unproblematic furnishing the precursors [142a] and [142b] in 58% and 48% respectively.

We next concentrated on the generation of amidyl radicals from these precursors. The method of Walton was used as a guideline for the radical generation.

3.3. Radical generation

From the work of Walton and co-workers, it was shown that carbon radicals could be generated from the cyclohexadiene carboxylate precursors by heating with di-*tert*-butyl peroxide in sealed tube of *tert*-butyl benzene solution or benzene at 140 °C. Consequently we utilised similar conditions for the reactions of our new precursors. The reactions can be seen as Scheme 3.10.

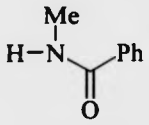


[142] [146] [147]

Scheme 3.10

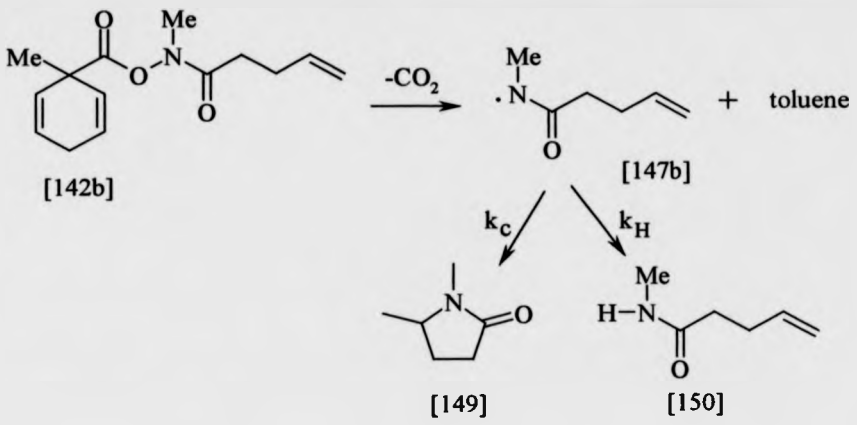
Initially, the reaction of precursor [142a] (R = Ph) was monitored by carring out the reaction in a sealable NMR tube. Hence, 0.2 equivalents of di-*tert*-butyl peroxide, $(t\text{-BuO})_2$, was applied as a radical initiator in degassed d_6-benzene solution with the initial concentration of the precursor at 0.7M. The reaction was heated in an oil bath at 80 °C for 3 hours. The NMR showed that there was only starting material in reaction. Therefore, the temperature was increased to 120 °C and the reaction was left for 24 hours. The resulting spectra showed that the reaction had not changed. Heating at an even higher temperature for a longer time (140 °C, 48 hours) still only indicated starting precursor in the reaction. The results suggest that the intermediate

cyclohexadienyl radical [146a] did not undergo decarboxylation to give the corresponding radical [147a] under these conditions. The reaction was modified by reducing the concentration of substrate to 0.12 M and reacting in *tert*-butyl benzene solution in a sealed tube at 140 °C. After 24 hours, the solvent was removed by vacuum distillation. The NMR spectra of the residue showed that there were still the starting carboxylate [142a] together with the amide [148a]. Purification further by silica gel column chromatography furnished the amide [148a] in 20% yield.



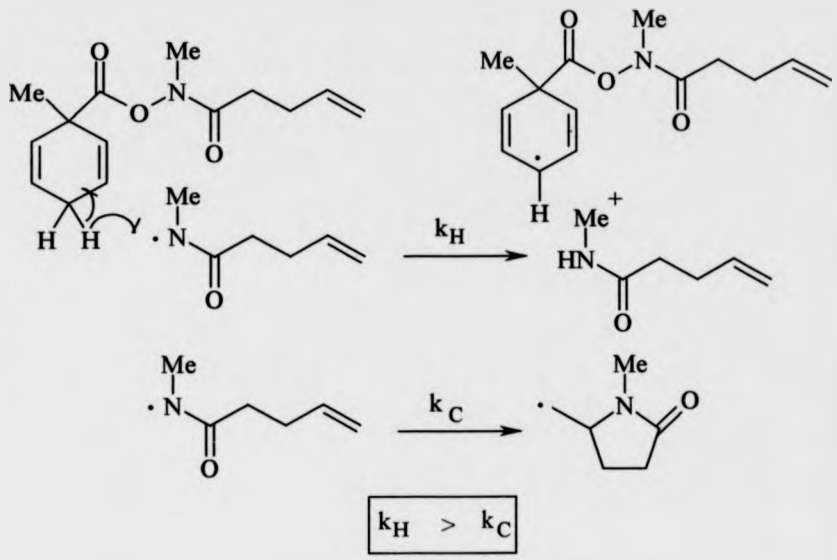
[148a]

Although the yield of the reduced product [148a] was low, we were satisfied to find condition that finally enabled amidyl radical generation. The product [148a] presumably arises from reduction of the generated amidyl radical by H abstraction from the starting carboxylate [142a]. We then carried out the reaction of carboxylate [142b] under these conditions. Hence, [142b] was heated at 140 °C for 48 hours in the presence of di-*tert*-butyl peroxide 0.5 equivalent. The radical generation and chain reaction was expected to proceed as shown in Scheme 3.11.



Scheme 3.11

However, upon analysis of the reaction there was only a mixture of starting carboxylate [142b] and the reduced product [150] with no cyclised product [149] detected. Consequently it can be concluded that the amidyl radical [147b] was produced in the reaction but that it underwent hydrogen abstraction more rapidly than cyclisation. As a consequence, the rate constant for hydrogen abstraction (k_H) must be much higher than the rate constant for cyclisation (k_C) at the concentration studied. Reduction of the electrophilic amidyl radical by H-abstraction from the electron rich allylic hydrogen atom in [142b] is the likely explanation for the facile reduction process.



Scheme 3.12

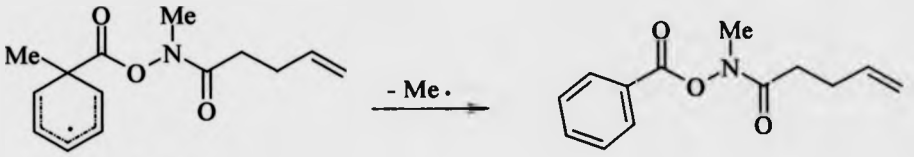
Consequently one approach to facilitate cyclisation might be by decreasing the concentration of starting carboxylate [142b] to maximise the life time of the amidyl radical.

3.4. Concentration effects

As mentioned earlier, the concentration of the starting carboxylate [142b] will affect the radical chain reaction due to competitive reduction of the amidyl radical prior to cyclisation by the carboxylate [142b] with contains bisallylic hydrogens. These

hydrogens can be readily abstracted by the amidyl radical [147b] to produce the reduced product [150]. It was assumed that at low concentration of the starting carboxylate [142b], this rate of hydrogen abstraction would be slower and that under these conditions, the radical [147b] could undergo cyclisation to afford the desired cyclised product [149]. All the reactions were previously carried out in a sealed tube and this limits the application of low concentrations (high solvent volumes are required). The reaction was therefore carried out in refluxing toluene in the presence of benzoyl peroxide, 0.5 equivalent. The concentration of starting carboxylate [142b] was 0.02 M and the syringe pump technique was used to apply the initiator. Hence, benzoyl peroxide in toluene was slowly added to the refluxing solution of [142b] in toluene over 5 hours *via* syringe pump. After refluxing for a further 17 hour, the toluene was removed in vacuo and the crude NMR spectra showed that there were only reduced product [150] together with the staring carboxylate [142b] as before. From this experiment, we were satisfied that it was possible to generate the amidyl radical without the need for high teperature (140°C) in a sealed tube. However under these conditions, the radical [147b] still underwent hydrogen abstraction before cyclisation (i.e. the concentration of [142b] was still too high for efficient cyclisation). The concentration of carboxylate [142b] was consequently reduced further by slowly adding the starting carboxylate [142b] (0.02M) and benzoyl peroxide into the refluxing toluene. With this condition, the concentration of [142b] would be very low. The crude NMR spectra showed that major product was the reduced product [150] together with a trace amount of cyclised product [149] and benzyl ester [151] as a by-product. All the starting carboxylate [142b] was consumed.

The residue was then purified by flash column chromatography. The reduced product [151] and cyclised product [149] were both collected together in 24% yield since they could not be fully separated. The ratio of [151] to [149] was 93:7. The ratio was detected from the integrations of N-methyl groups in the ^{1}H NMR spectra. The proton chemical shift of N-Me in reduced product and in cyclised product appeared at 2.79 and 2.89 ppm respectively. In addition, 5 % of benzyl ester [151] was also produced as a by-product. The formation of [151] can be explained by methyl radical loss from the intermediate radical [146b] (Scheme 3.13).



[146b] [151]

Scheme 3.13

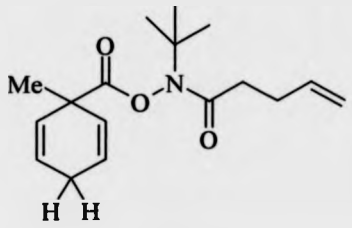
In conclusion, the application of cyclohexadienyl carboxylates as substrates for the cyclisation of amidyl radicals was not practical enough even at low concentration to be synthetically useful.

3.5. Inductive effect

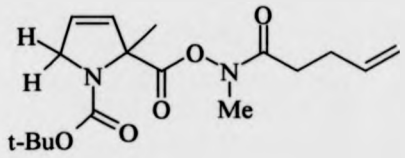
The formation of large quantities of reduction products in the above reactions is likely due to the fact that the electrophilic amidyl radical is electronically set up to abstract the electron rich hydrogen atom found in the substrate. The rate of reduction of the

amidyl radical may be slowed if the hydrogen atoms were made less electron rich or if the amidyl radical itself was more nucleophilic. The importance of electronic matching in hydrogen abstraction reaction has been known for some time.

Consequently we decided to investigate the cyclisation of amidyl radicals generated from [152] and [153].



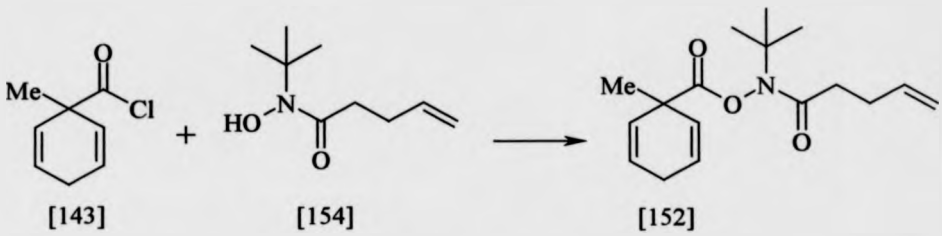
[152]



[153]

In the former the N-methyl group found in [142b] would be replaced with a N-*tert*-butyl group in cyclohexadiene carboxylate [152]. The *tert*-butyl group is an electron donating group which would make the nitrogen radical more nucleophilic. In addition the steric bulk at nitrogen would also be likely to slow the bimolecular intermolecular reduction reaction. In the latter precursor [153], the cyclic system of [142b] would be replaced with that of a nitrogen heterocycle. The inductive effect of the nitrogen group in this new cyclic system would make the allylic hydrogen atom less electron rich than in the cyclohexadienyl system found in [142b] and [152].

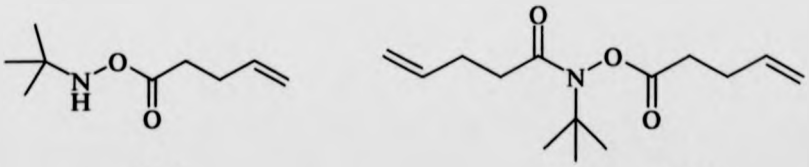
Our first experiments involved the preparation of cyclohexadienyl precursor [152]. The retrosynthetic analysis was similar to that for [142b] with carboxyl chloride [143] being reacted with hydroxamic acid [154] as shown in Scheme 3.14.



[143] [154] [152]

Scheme 3.14

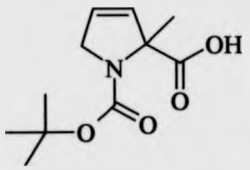
Therefore, the starting *tert*-butyl hydroxamic acid [154] was prepared. N-*tert*-butyl hydroxylamine hydrochloride and triethylamine was reacted with penten-4-oyl chloride in diethyl ether for 24 hours. Unfortunately, it was found that only a very small amount of the desired hydroxyamide [154] was formed. Purification by column chromatography, furnished hydroxamic acid [154] in 3% yield. Unexpectedly, a compound [155] was formed as the major product in 20% together with the bisacylated compound [156] in 4% yield.



[155] [156]

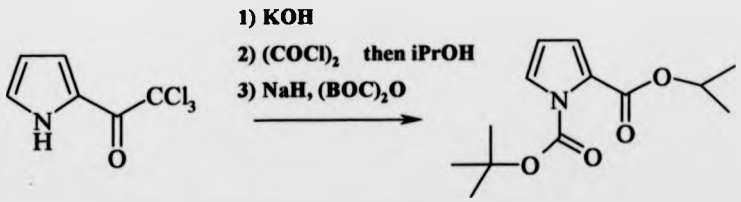
Normally, under neutral conditions, the amine functional group in hydroxylamines is more nucleophilic than the hydroxy group. This normally means that the nitrogen atom is the most reactive site in the reaction of hydroxylamines with electrophilic compounds. However, in this case the bulky *tert*-butyl group slows the nucleophilic addition at the nitrogen leaving the less hindered hydroxy group to undergo addition with the acid chloride instead. Due to the difficulty of preparation of hydroxylamide [154], we consequently switched attention to the preparation of the alternative precursor [153]. In this precursor, an important aspect is the preparation of nitrogen heterocyclic fragment (dihydropyrrole derivative). A literature survey found that the reduction of pyrrole to the corresponding pyrroline skeleton has been investigated by Donohoe and co-workers.[83] They were interested in facilitating the reduction of pyrroles using the Birch reduction (sodium metal in liquid ammonia). However, the pyrrole nucleus is electron-rich (high nucleophilicity) and this fact is generally a disadvantage when one is considering the addition of electrons to the aromatic system. In addition, the presence of an acidic hydrogen atom on the pyrrole nitrogen (p*Ka* ~17) presents the opportunity of deprotonation under the reducing conditions employed. Therefore, placing an electron withdrawing group in the 2-position of the pyrrole should control the regiochemistry of the reduction and also provide an opportunity for reductive alkylation. In addition, a lack of regioselectivity in the site of protonation of the radical-anion resulting from the addition of an electron to the aromatic system would be alleviated by placing a nitrogen protecting group that was also capable of withdrawing electrons. With this protecting group, the reaction would promote reduction of the aromatic portion of the molecule.

Consequently the dihydropyrrole carboxylic acid [157] was prepared by this methodology. [83b]



[157]

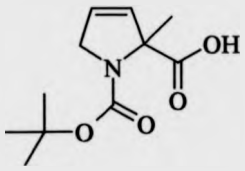
Using this approach, the Birch reduction substrate, isopropyl ester [158], was prepared in three steps (Scheme 3.13). Firstly, commercially available trichloroacetyl pyrrole was reacted with potassium hydroxide to afford the potassium salt. Secondly, an oxalyl chloride was then applied to the salt to give the corresponding acid chloride which was then dissolved in isopropyl alcohol. This step provided the pyrrole isopropyl ester in a good yield (85%). Finally, the nitrogen was protected using $(BOC)_2O$ (62% yield).



[158]

Scheme 3.15

Consequently the dihydropyrrole carboxylic acid [157] was prepared by this methodology. [83b]



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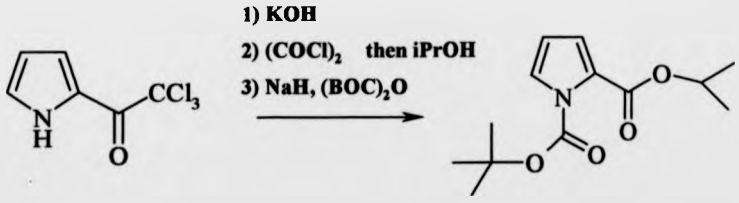
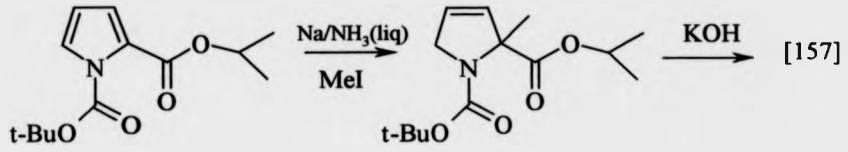


[158]

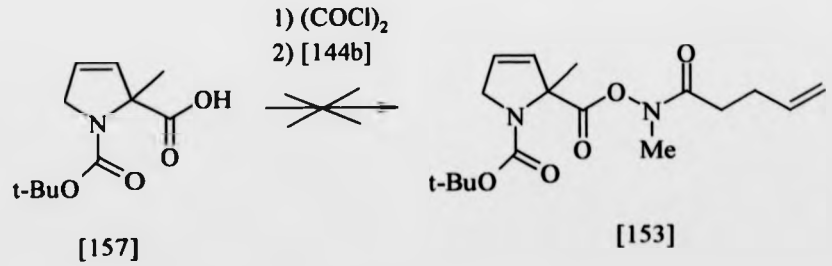
Scheme 3.15

With the pyrrole [158] in hand, the Birch reduction and methylation of ester [158] with sodium metal in liquid ammonia solvent was attempted and furnished the pyrroline ester in 23% yield. This ester was then hydrolysed by potassium hydroxide to afford the acid [157] (Scheme 3.16).



Scheme 3.16

The acid chloride was then prepared from this acid and was reacted with hydroxylamide [144b]. However, only starting materials were reisolated from the reaction mixture (Scheme 3.17)



Scheme 3.17

Apart from the failure of the last step reported above the overall length of the synthesis of [157] made preparation of large quantities of the desired precursors particularly difficult.

In summary, the preparations of precursors [152] and [153] were not successful and as a consequence attempts to optimise the cyclisation by inductive effects of precursors could not be investigated.

3.6. Conclusion

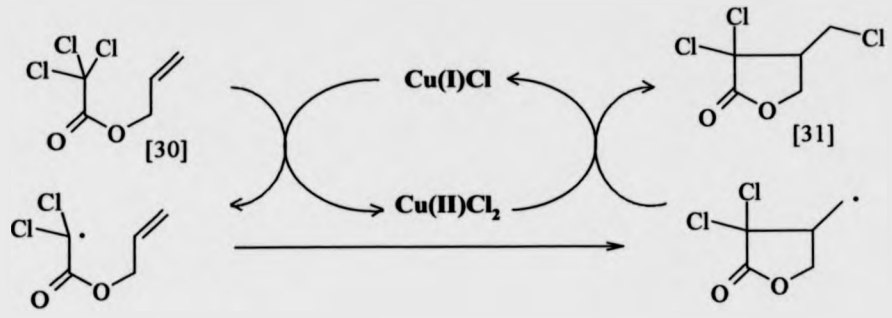
It was possible to generate amidyl radicals from cyclohexadienyl functionalised hydroxamic acid derivatives using peroxides as initiators. However, it was not possible to mediate cyclisations of these generated radicals in any useful synthesis. This was primarily due to the rapid reduction of the amidyl radical by hydrogen abstraction from the initial cyclohexadienyl system.

CHAPTER 4

Atom transfer cyclisation of allyl trichloroacetate

4.1. Introduction

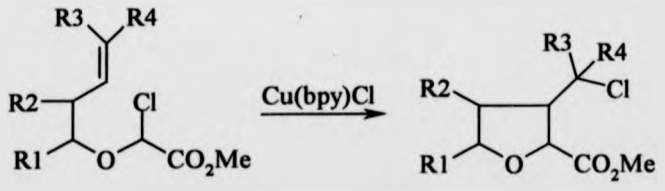
Transition metal-catalysed radical cyclisations have received considerable attention in organic synthesis. The atom transfer cyclisation of ω-haloolefins is currently emerging as a valuable tool for the construction of carbo- and heterocyclic molecules. Recently, the cyclisations of allyl trichloroacetate by copper catalysts have been reported by Nagashima and co-workers.[26,27] This work has shown that γ-lactone [31] can be obtained from allyl trichloroacetate by several cuprous salts in acetonitrile however large amounts of catalysts (10-30%) and high temperatures were required to attain high yields of the product. Many atom transfer cyclisation approaches use transition-metal complexes to promote carbon-carbon bond formation. Transition metals able to function as halogen carriers, with an available $n + 1$ oxidation state, such as the Cu(I)-Cu(II) couple are normally useful (Scheme 4.1).



Scheme 4.1

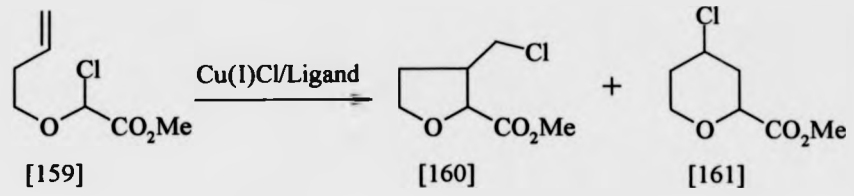
In addition bipyridine was used in the cyclisation as a co-catalyst. They found that the rate of the cyclisation using Cu(I)Cl and bipyridine was four times as fast as with Cu(I)Cl alone. It was suggested the active catalyst was due to the formation of a Cu(I)Cl (bipyridine) complex in the reaction.[27]

Another example is the chlorine-transfer radical cyclisation of 2-(3-alken-1-oxy)-2-chloroacetates. Speckamp and co-workers have reported that Cu(I)Cl (bipyridine) can be used as an effective catalyst in the formation of new C-C bonds in atom-transfer radical cyclisation to give 2-carbomethoxy-3-(1-chloroalkyl)-substituted tetrahydrofurans (Scheme 4.2). [84]



Scheme 4.2

In 1992, this group published that the choice of ligand for the copper complex was very important for the regiochemical outcome of the cyclisation of O-(butyl-3-enyl)-α-chlorogylcolic acid methyl ester (Scheme 4.3).



Scheme 4.3

When the ester [159] was heated at reflux in 1,2-dichloroethane in the presence of copper(I) chloride-2,2'-bipyridine for 18 hours, the 5-*exo* cyclised product [160] was isolated in 73% yield. The 6-*endo* cyclised product [161] was found in 7% as a minor product. In the other hand, the use of 6,6'-dimethyl-2,2'-bipyridine as the ligand changed the regioselectivity in favour of *endo*-cyclisation. Only the *endo*-cyclised product was isolated in 67% yield.

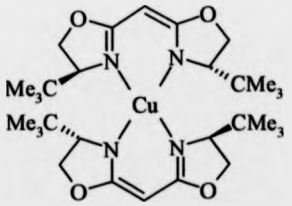
The chemistry of the copper (I) complex reaction may be described by the equilibrium shown in equation 4.1.[85]

$$R{-}X \;+\; Cu(I)X \rightleftharpoons R\cdot \;+\; Cu(II)X_2$$

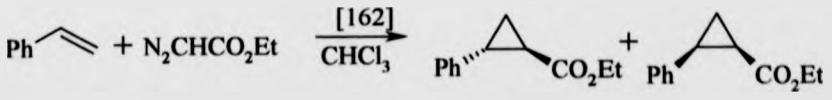
Equation 4.1

The position of the equilibrium is important in controlling the reaction. If the copper (I) complex is too easily oxidised and, the *n*+1 oxidation state is too stable then the equilibrium may lie too far to the right resulting in a relatively large concentration of free radicals leading to radical-radical combination. Conversely, if the metal is not able to increase its oxidation number the equilibrium lies to the left and no reaction occurs.

A survey of the literature shows that copper complexes containing α-diimines having the N=C-C=N skeleton as ligands are finding increasing use as catalyst for a wide range of organic reactions. [86,87] For example, copper (I) bis (oxazoline) complex [162] has been utilised in the enantioselective cyclopropanation of olefins by ethyl diazoacetate (Scheme 4.4). [86]



[162]

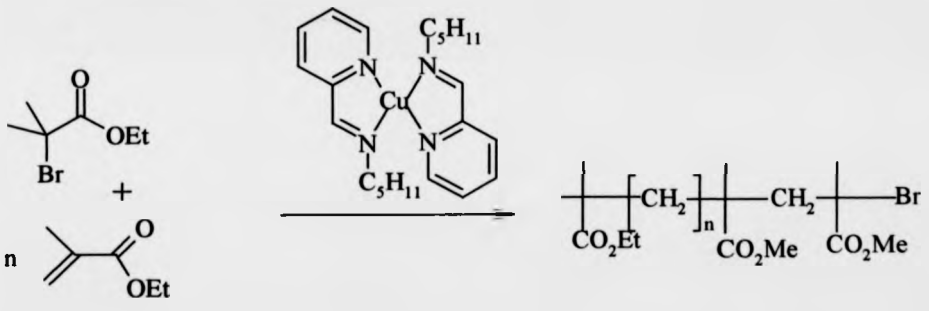


[163a] [163b]

Scheme 4.4

It was reported that [162] formed an effective catalyst for enantioselective cyclopropanation. The enantioselection was found to be 88% and 83% *ee* for ethyl cyclopropanecarboxylates [163a] and [163b] respectively.

The radical polymerisation of methyl methacrylate is one example where α-diimines have been used as ligands to form copper complexes to carry out atom transfer reactions.[87] This polymerisation was carried out with ethyl 2-methyl-2-bromopropionate as an initiator in conjunction with N-pentyl-2-pyridyl-methanimine and copper (I) bromide in xylene solution at 90 °C (Scheme 4.5).



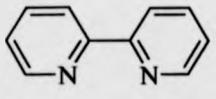
Scheme 4.5

In our work, we were interested in using copper complexes as catalysts to mediate cyclisations to give heterocyclic molecules. The choice of ligand is crucial in controlling the position of the equilibrium by acting as either electron donors or acceptors to the metal. In order to optimise the catalyst ligand combination, it would be useful to test a whole range of related ligands to compare their efficiency. However, preparing analogues of bipyridine is not an easy undertaking and

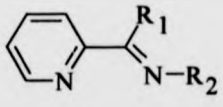
consequently we decided to investigate the effects of the pyridylmethanimine ligand on cyclisation reactions as they are much easier to prepare. These chelating diimine ligands have a conjugated π system which is able to accept electron density from the metal and hence serves to stabilise low oxidation states.

4.2. Initial investigations

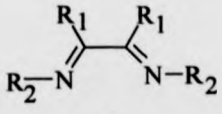
As mentioned earlier, bipyridine has been used as a ligand in the copper mediated the cyclisation of allyl trichloroacetate[27] and of 2-(3-alken-1-oxy)-2-chloroacetates.[84] Consequently, we proposed that bipyridine might be replaced with other α-diimines having the N=C-C=N skeleton. We were interested in ligands of type A and B, where R_1 and R_2 = H, allyl, aryl, substituted alkyl/aryl. Both A and B have the capability of accepting electron density into their low lying π* orbital and they have been reported to be superior to bipyridine in stabilising and solubilising copper (I) halides[85] since copper (I) halides are very insoluble in organic solvents.



Bipyridine

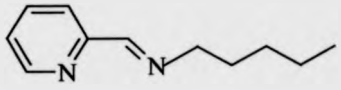


A



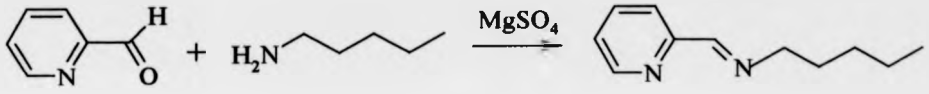
B

Initially, the first ligand we investigated was N-pentyl-2-pyridylmethanimine [164] which has been used before as a ligand to form a copper complexes used in the radical polymerisation of methyl methacrylate. [87]



[164]

Ligand, [164], was simply prepared from commercially 2-pyridine carboxaldehyde and pentylamine (Scheme 4.6)

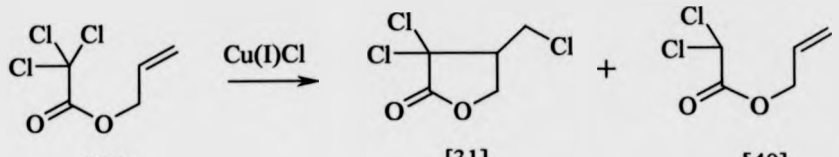


[164]

Scheme 4.6

The reaction was carried out at room temperature in the presence of excess magnesium sulphate to remove water. Purification by vacuum distillation gave the imine [164] in 62% yield.

Following the procedure of Nagashima and co-worker[27], we investigated the cyclisation of allyl trichloroacetate [30] (Scheme 4.7).



[30] [31] [40]

Scheme 4.7

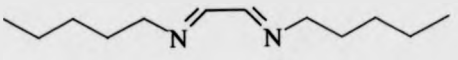
Hence, to a solution of [30] in acetonitrile (0.13M) was added 30mol% of CuCl and ligand [164]. The mixture was heated in a sealed tube. It has been reported that the conversion of allyl trichloroacetate [30] with CuCl alone goes to completion (99%) after heating for 16 hours. In order to compare the efficiency of a range of ligands we therefore stopped the reaction before that time (4 hours) and compared their conversions. The conversion of allyl trichloroacetate to product [31] was determined either by GC or ^{1}H NMR analysis of the crude mixture. We initially compared the efficiency of ligand [164] with that of bipyridine in the cyclisation reaction. It was found that the γ-lactone [31] was produced together with a small amount of allyl dichloroacetate [40] and a significant amount of high molecular weight compounds (telomers). In each case (table 4.1), the former by-product was produced from the reduction of allyl trichloroacetate whereas the latter was formed by intermolecular polymerisation (telomerisation). The result of the first three reactions is shown in table 4.1.

Entry	Ligand	Conversion(%)	Cyclised product(%)
1	-	31	22
2	Bipy	53	18
3	[164]	63	43

Table 4.1. Cyclisation of allyl trichloroacetate at 110 °C in sealed tube (4 hours) in ACN in the presence of ligand [164], bipyridine and without ligand use

It was shown that bipyridine and ligand [164] gave good conversions, 53% and 63% respectively whereas the reaction without any ligand only gave a conversion of 31%. However, telomerisation was more important in the reaction with bipyridine and only 18% of the desired γ-lactone was isolated. The reaction without ligand provided a cleaner reaction with the cyclised product in 22% whereas ligand [164] gave the highest yield of cyclised product (43%). Therefore, the cyclisation with the new catalyst prepared from ligand [164] and CuCl provided the best result in both conversion and isolated yield of cyclised product.

The success of using ligand [164] prompted us to evaluate the effect of ligands of type B in the cyclisation reaction. 1,4-Dipentyl-1,4-diazobuta-1,3-diene, [165], was therefore prepared by the reaction of glyoxal with pentylamine.[85] As a comparison the saturated analogue N,N,N',N'-tetramethylethylenediamine (TMEDA) was also used as a ligand. Although TMEDA does not have the N=C-C=N skeleton, it also has nitrogen donor atoms which contain sp^3-hybridised nitrogen atoms,[88] and has been previously reported by Ghelfi [89] to be an effective catalyst system in the Cu(I)Cl mediated radical cyclisation of N-allyl-N-benzyl-2,2-dihaloamides to give 2-pyrrolidinones (γ-lactams).



[165]

TMEDA

The evaluations of these ligands was carried out under the same conditions as those previous described. Both reactions afforded the desired lactone [31] along with telomers as the main by-product. The results of these cyclisations are shown in table 4.2.

Entry	Ligand	Conversion(%)	Cyclised product(%)
1	[165]	52	36
2	TMEDA	46	17

Table 4.2. Cyclisation of allyl trichloroacetate at 110 °C in sealed tube (4 hours) in the presence of ligand [165] and TMEDA

Both ligands [165] and TMEDA gave the conversion similar to bipyridine (52% and 46% respectively). However, the low yield arising from the use of TMEDA (17%) was a consequence of considerable telomerisation.

In conclusion, ligands [164] or [165] with CuCl provided a more effective catalyst system for the cyclisation of allyl trichloroacetate compared to the previously published ligands bipyridine or TMEDA. However, competing telomerisation of the starting allyl trichloroacetate was a major problem in all the reactions. A summary of the results is shown in Figure 4.1.

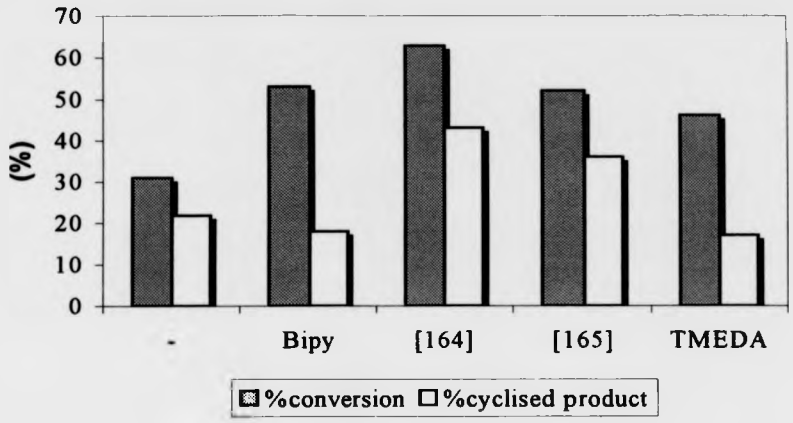


Figure 4.1. The conversion of starting allyl trichloroacetate and yield of γ-lactone in the cyclisation.

4.3. Optimisation

One disadvantage with all of the previous reaction was that there were carried out at 110 °C in acetonitrile in a sealed tube. It would be a more convenient procedure if the cyclisation could be conducted at reflux without the need to use sealed tube techniques. Consequently, the reaction was carried out using a number of different conditions. First of all, the reactions were conducted in refluxing acetonitrile solution and were monitored to investigate how the rate of the reaction varied with time. A 0.13M solution of starting allyl trichloroacetate was heated with CuCl-[164] 30mol%. The conversions were then determined by GC. It was found that after an initial fast reaction rate during the first 2 hours, the reaction slowed down considerably (see

Figure 4.2). The reaction was completed after 20 hours at this temperature, thus confirming that it was possible to mediate the cyclisation at lower temperatures.

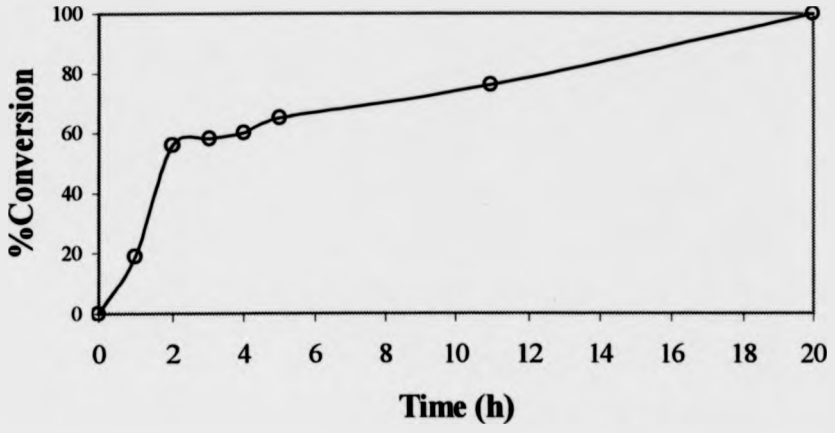


Figure 4.2. The reaction of allyl trichloroacetate conducted at 95°C in acetonitrile solution with the presence of 30mol% CuCl-[164]

In order to optimise the reaction further we next evaluated the effect of a range of changes.

4.3.1. Effect of ligand concentration

4.3.2. Effect of catalyst concentration

4.3.3. Effect of substrate concentration

4.3.4. Effect of solvent.

4.3.1. Effect of ligand concentration (equivalents to CuCl)

The reaction was carried out in refluxing acetonitrile solution (95°C) for 4 hours. Bipyridine, [164], [165] and TMEDA were used as ligands. A 0.13M solution of allyl trichloroacetate was used with 30mol% of CuCl and either 30, 60 or 90mole% of ligand. The results are showed in Table 4.3 and the comparison of all reactions is shown in Figure 4.3.

Entry	Ligand	Ligand conc. (mol%)	Conversion (%)	Cyclised product (%)
1	Bipy	30	33	20
2		60	67	30
3		90	61	25
4	[164]	30	45	23
5		60	61	37
6		90	55	29
7	[165]	30	46	26
8		60	90	38
9		90	70	36
10	TMEDA	30	50	22
11		60	100	23
12		90	88	35

Table 4.3. Effect of ligand concentration in the cyclisation of allyl trichloroacetate

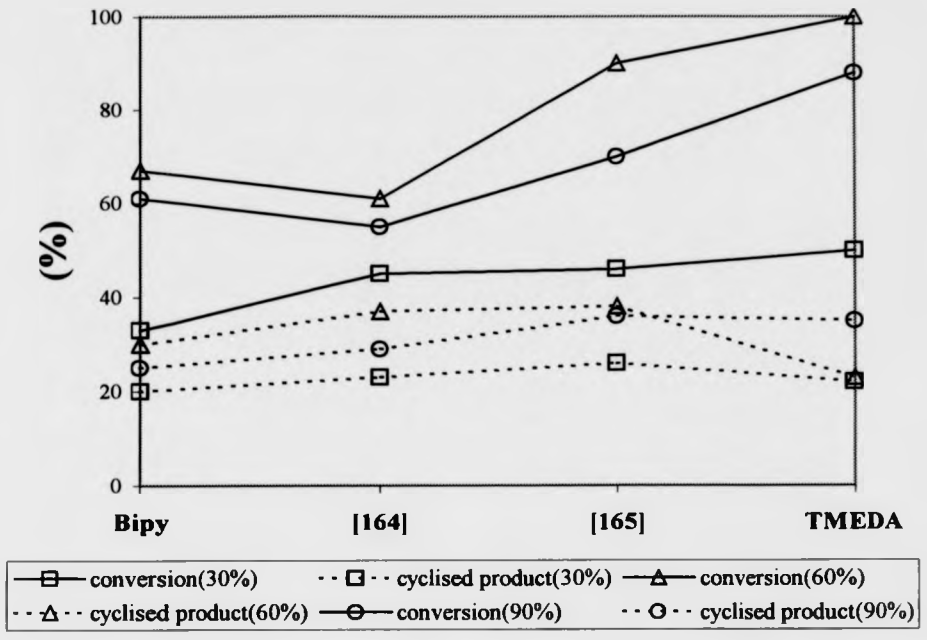
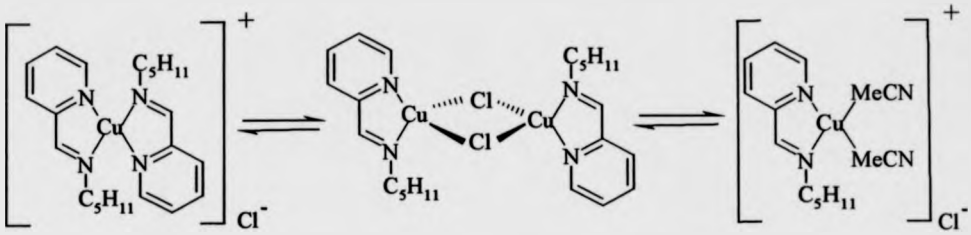


Figure 4.3 Effect of ligand concentration in the cyclisation of allyl trichloroacetate

The results clearly show that the use of only 30mol% (1eq of ligand to CuCl) with all the ligands gave the lowest conversions and yields. Most reactions provided similar conversions at about 45% whereas the bipyridine ligand gave the lowest conversion at only 33%. When the concentration of ligands is higher (60mol% and 90mol%, 2eq and 3eq to CuCl), the conversions and yields of cyclised products were increased. Using 60mol% of ligands provided the highest conversion in all cases suggesting that the optimum ratio is 2:1 bidentate ligand : copper for the active catalyst. When the concentration of ligands is increased to 90mol%, the conversions and yields slightly decrease. With the latter two concentrations (60 and 90mol%), both bipyridine and

[164] afforded similar results giving about 60% conversion. The use of ligand [165] and TMEDA provide higher conversions. Interestingly, when 60% TMEDA was used, the conversion went up to 100%, however yields of the cyclised products were found to be fairly low (about 20-37%) with telomerisation predominating. Therefore, it was not a practically useful application. However, the use of 60mol% [164] gave the best result since it provided the highest cyclised product in 37%. The optimum ratio of 2:1 bidentate ligand : CuCl suggests that the active catalyst may be a four-coordinated complex, [166]. X-ray structures of related 2:1 complexes have been published and indicated a regular tetrahedral arrangement of ligands around copper. Therefore, with CuCl and two ligand equivalents it is likely that the effective copper complex catalyst has a similar structure with one ligand equivalent to CuCl. The reaction is not as efficient and there are likely to be two possible complexes that may be the active catalysts (the binuclear and mononuclear complexes). The former complex would be formed by chloride bridging to give a bridged dimer [167]. Alternatively, acetonitrile may suppress the formation of the bridged dimer by rupture of halogen bridging followed by coordination of acetonitrile molecules to form a [Cu(ligand)-Cl$(MeCN)_2$] complex [168]. [90]

It is possible that all three complexes [166], [167] and [168] are in equilibrium in solution. The position of this equilibrium will be dependent as the amount of ligand present. This might explain why the rates of reactions are so different with varying amounts of ligands.



[166] [167] [168]

4.3.2.Effect of catalyst concentration

Having established that the best yields of cyclised products were obtained using a 2:1 equivalent of ligand pyridylmethanimine [164] to CuCl, we next investigated the effect of the amount of this catalyst on the conversion and yield of the products. The reactions were carried out in refluxing acetonitrile solution (95°C) for 4 hours. The concentration of allyl trichloroacetate was 0.13M, while the amount of CuCl was varied from 5, 30, 60, 100mol% with 2 equivalents of ligand [164]. The results are shown in Table 4.4.

Entry	CuCl-[164] conc. (%)	Conversion (%)	Cyclised product (%)
1	5	25	17
2	30	61	37
3	60	65	29
4	100	69	13

Table 4.4. Effect of catalysed concentration in the cyclisation of allyl trichloroacetate

The reactions gave the expected cyclised product, γ-lactone [31], and the high molecular weight compounds; telomers. The results from table 4.4 show that low concentrations of catalyst (5%) provided fairly modest conversions (25%) and product yields (17%). When the concentration was increased (30%, 60% and 100%) the conversion also increased to 61-69%. With one equivalent of catalyst (100%), the reaction gave the best conversion in 69%, however, this reaction provided a very low yield of cyclised product (13%). This may be because of the high concentration of allyl dichloroacetate radical produced with such high concentrations of catalyst (i.e. the radical did not only undergo cyclisation and telomerisation as expected but could also undergo radical-radical combination to give the higher molecular weight compounds which were detected by mass spectroscopy). In conclusion, the optimum concentration of catalyst was found to be 30mol% giving the best yields of product with acceptable conversion rate.

4.3.3.Effect of substrate concentration

The reaction was carried out in refluxing acetonitrile solution (95°C) for 4 hours with 30%mole of CuCl-[164]$_2$ as a catalyst. The effect of substrate concentration was studied at a number of concentrations of allyl trichloroacetate (0.065, 0.13, 0.26 and 0.39M). The results are shown in Table 4.5.

Entry	Substrate conc. (M)	Conversion (%)	Cyclised product (%)
1	0.065	58	32
2	0.13	61	37
3	0.26	59	17
4	0.39	51	15

Table 4.5. Effect of substrate concentration in the cyclisation of allyl trichloroacetate

Table 4.5. shows that the conversions of allyl trichloroacetate from the reactions were pretty similar however the yield of cyclised products varied considerably. With 0.13M, providing the best conversion (61%) and yield (37%). At higher concentrations of substrate (e.g. 0.26 and 0.39M), the radical is more likely to undergo intermolecular addition to afford telomers and this can be seen in the low yield for cyclisation. Moreover, at these higher concentrations, significant amount of allyl dichloroactate from reduction was also detected. The latter by-product is formed by hydrogen abstraction from the solvent or ligand.

4.3.4.Effect of solvent.

All the experiments carried out previously in this chapter used acetonitrile as solvent for the cyclisation reaction. This is a co-ordinating solvent known to dissolve CuCl (to give $Cu(MeCN)_4Cl$). However, we also investigated the use of the non-co-ordinating solvent (toluene) in the reactions.

The reactions were carried out in either refluxing acetonitrile (95°C) or toluene solution (110°C) for 4 hours, with 0.13M of allyl trichloroacetate was use with CuCl alone or using the CuCl-[164] catalyst combination. The comparison of reactions using different solvents is shown in table 4.6.

Entry	Catalyst	Solvent	Conversion (%)	Cyclised product (%)
1	CuCl	MeCN	32	23
2	CuCl	Toluene	-	-
3	CuCl-[164]	MeCN	45	23
4	CuCl-[164]	Toluene	65	45

Table 4.6. Effect of solvent in the cyclisation of allyl trichloroacetate

From the table 4.6, we can see that with CuCl alone the reaction gave 32% conversion in acetonitrile whereas no reaction took place at all in toluene solution. This is because whereas acetonitrile dissolves CuCl to give a homogenous solution, CuCl is insoluble in toluene and a heterogenous mixture resulted. This indicated the importance of solubility of the copper catalyst system. Using CuCl-[164] as a catalyst, the reaction provided 45% and 65% conversion in acetonitrile and toluene solution respectively. Cyclised product was detected at 23% in acetonitrile solution and 45% in toluene solution. This showed that toluene solution with CuCl-[164] gave the better conversion and cyclised product yield. In conclusion, the reaction may be carried out in both acetonitrile and toluene using CuCl-[164] with the reaction being faster in toluene solution.

4.4. Conclusion

N-pentyl-2-pyridylmethanimine, [164], is an effective ligand in copper mediated atom transfer radical cyclisation of allyl trichloroacetate using Cu(I)Cl. The new active catalyst CuCl-[164] can be prepared *in situ* by mixing the two components. It is assumed that this catalyst consists of a Cu(I) species which formally abstract a chloride atom from the starting allyl trichloroacetate, [30], to furnish a dichloroacetate radical and a Cu(II) species. The radical attacks the alkene functionality leading to a new carbon radical which accepts a chlorine atom from the previously formed Cu(II) complex to give the functionalised γ-lactone, [31], and regenerates the Cu(I) species. This Cu(I) species can then undergo another catalytic cycle. The combination of CuCl and ligand [164] in a solvent containing allyl trichloroacetate leads to the formation of a red-brown solution which is probably due to the soluble CuCl-[164] complex. This red-brown solution is air sensitive and upon oxygen contamination gives an unactive light green solution.

Two equivalents of ligand with CuCl provided the most effective catalyst while the use of 30mol% of catalyst was essential for the success of the cyclisation. A lower yield of product was obtained if the amount of catalyst was lowered and this may be due to its gradual decomposition (a green solution was produced fairly quickly). The reaction was best carried out at a 0.065 to 0.13M solution in order to suppress telomerisation processes and intermolecular addition and reduction processes due to hydrogen abstraction reactions. At higher concentrations more telomers were

obtained. In toluene solution, the CuCl-[164] catalyst system provided faster reactions when compared with the same reaction in acetonitrile solution.

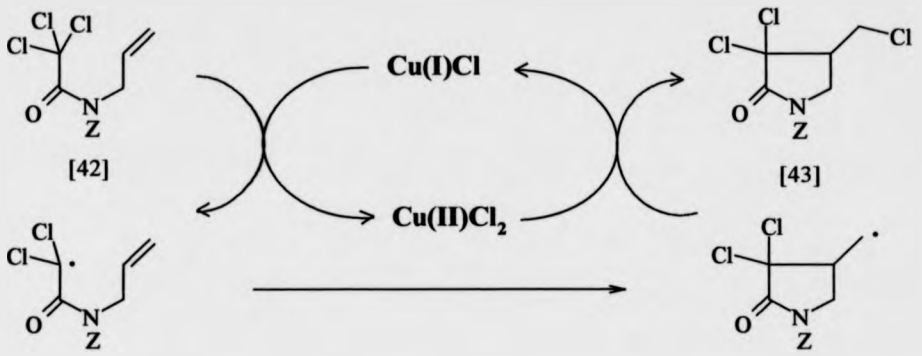
CHAPTER 5

Atom transfer cyclisation of N-allyl trichloroacetamides

5.1 Introduction

As mentioned earlier, the synthesis of γ-lactams can be carried out by transition metal-catalysed radical cyclisation (1.4.4.3) which has been used as an alternative to the usual tributyltin hydride method. Previous work has involved the atom transfer cyclisation of N-allyl iodoacetamides with palladium-catalysts. It was reported that the cyclisation proceeded in poor yields.[29] After this work, lactam ring synthsis using atom transfer methodology has been the subject of renewed interest over the last few years[26,27]. A number of low valent metal complexes have been used in cyclisations of α-haloamides having internal double bonds.

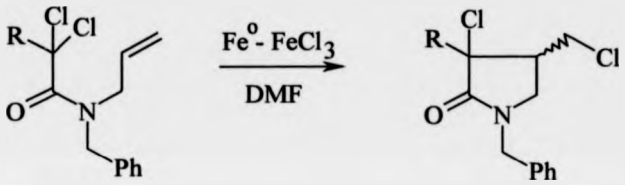
In 1984 [28] Nagashima and co-workers had established the cyclisation of N-allyl trichloroacetamide using copper or ruthenium based catalysts. As in the last chapter, the transition metal acts as a halogen carrier in which there is an equilibrium between n and n+1 oxidation states (Scheme 5.1).



Scheme 5.1

The effect of the nitrogen protecting group on the starting trichloroacetamides has been investigated.[29] Initially, they were interested in adding the substituents on the nitrogen in order to study the effect of them on the stereochemical outcome of the 1-buten-3-yl trichloroacetamide cyclisation. Interestingly, these nitrogen protecting groups did not only have an effect on the stereoselectivity of the cyclisation but also affected the rate and allowed the reactions to be carried out at lower temperatures. Normally, trichloroacetamide cyclisations were carried out at 80-140 °C using copper salts and ruthenium complexes. However, with the nitrogen protected, the reactions could take place at 50 °C. In addition, if the catalyst system contained copper(I) chloride and bipyridine or a bidentate amine such as TMEDA, the reaction could proceed even at –78 °C. At these low temperatures, the cyclisation provided good stereoselectivity. However, this new catalyst system did not catalyse the cyclisation of N-allyl trichloroacetamide (without nitrogen protection) at such a low temperature.

The use of Fe° -$FeCl_3$ as a catalyst system in the halogen atom transfer radical cyclisation of N-allyl-N-benzyl-2,2-dichloropropanamide was studied by Ghelfi and co-workers.[89] They have reported that Fe° promoted the transformation of [169] in good yield whereas the unprotected amide did not react even at 125 °C (Scheme 5.2). Furthermore, they found that disproportionation between $FeCl_3$ and Fe° afforded $FeCl_2$ which was another efficient reagent. This new reagent could promote halogen atom transfer radical addition and the intermediate cyclic radical could now be effectively trapped through a ligand-transfer from $FeCl_3$, not by H removal from solvent. DMF was the suitable solvent for this cyclisation.



[169] [170]

Scheme 5.2

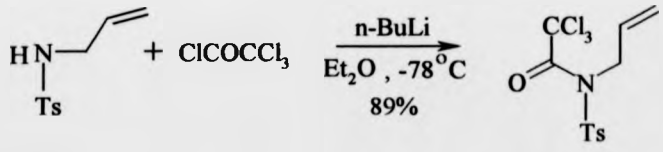
The benzyl group was replaced with a number of other protecting groups such as phenyl, alkyl and tosyl. It was found that with none of them was the observed selectivity significantly better than with the benzyl group. Furthermore, using sulfonyl protection afforded relatively high amounts of N-allyl-2-chloroacetamide and N-allyl-acetamide as by-products.

In chapter 2 and 3, we described the synthesis of heterocycles using nitrogen centered radical to form C-N bonds. Consequently we investigated whether we could make

nitrogen heterocycles using atom transfer radical cyclisations. We initially focussed our investigations into the cyclisation of N-allyl trichloroacetamides using our catalyst system (CuCl and N-pentyl-2-pyridylmethanimine).

5.2 Initial investigations

Initially, the comparison between the effectiveness of N-pentyl-2-pyridylmethylanimine [164] and the previously reported bipyridine ligand for the cyclisation of an amide [172] was investigated. Therefore, the starting N-allyl N-tosyl trichloroacetamide [172] was prepare in 89% by reacting trichloroacetamide with N-allyl-N-tosylamide [171] prepared from the reaction between allylamide and p-toluenesulphonyl chloride (Scheme 5.3).[32]

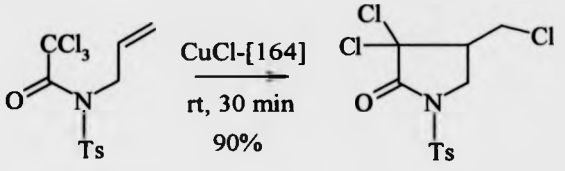


[171] [172]

Scheme 5.3

Subsequently, our first attempt was the cyclisation of the amide [172] in the presence of CuCl-[164] catalyst system. The reaction was carried out in acetonitrile solution at room temperature for 30 minutes with 30mol% of CuCl and ligand [164]. The

reaction was worked up by passing the crude solution through a short silica gel column and eluting with dichloromethane. This gave [173] in 90% yield (Scheme 5.4).



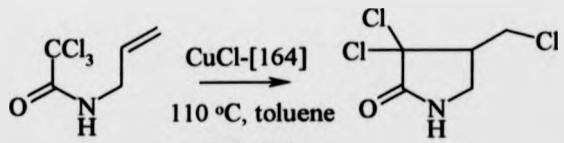
[172] [173]

Scheme 5.4

In order to compare the effectiveness of the ligand [164] with bipyridine, the amide [172] was treated with both catalyst systems at 0 °C for 30 minutes. At this low temperature, the reactions did not go to completion and the conversions of [172] in the two catalyst systems were compared. It was found that for the CuCl-[164] system, the conversion was 78% but the CuCl-bipyridine system was slightly less efficient giving 65% conversion. Both reactions proceed without telomerisation and no reduced products were observed. These results indicated that CuCl-[164] catalyst system could be used in the cyclisation of amide [172] as well as esters. Therefore, imine [164] was used as a ligand in all cyclisations in this chapter.

5.3 Cyclisations of N-allyl trichloroacetamide [174]

As mentioned in 5.1, the cyclisation of N-allyl trichloroacetamide has been carried out at high temperature 110 °C and 140 °C in the presence of $RuCl_2(PPh_3)_3$ and CuCl respectively.[28] Consequently, we attempted the cyclisation at a lower temperature by treatment with CuCl-[164] at room temperature. Unfortunately, it was found that this amide underwent cyclisation only at high temperature (110 °C) with 30% mole of CuCl-[164] in refluxing toluene solution for 24 hours (Scheme 5.5). However, this CuCl-[164] mediated cyclisation afforded a better yield of product [175] when compared to the previous literature procedures using $RuCl_2(PPh_3)_3$ and CuCl catalyst cyclisations. In our attempt, the reaction gave 76% yield of cyclised product whereas $RuCl_2(PPh_3)_3$ and CuCl gave only 52% and 57% yield respectively.[28] In conclusion, it was found that the cyclisation of the amide [174] using CuCl-[164] catalyst system in toluene solution gave the desired cyclised products in a good yields but high temperature conditions were needed in the cyclisation. Furthermore, the reaction was very clean and the metal complex was easily removed by a short silica gel column chromatography.

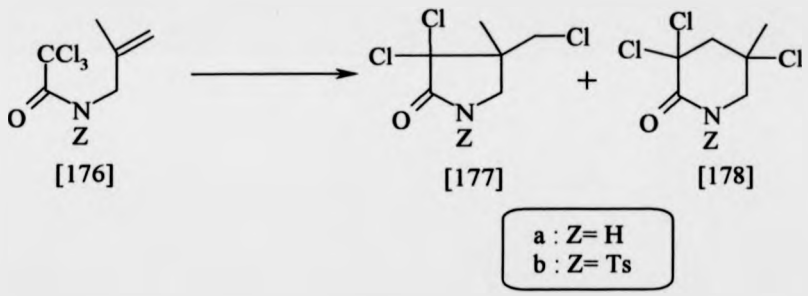


[174] [175]

Scheme 5.5

5.4 Cyclisations of N-2-methyl allyl trichloroacetamide and N-2-methyl allyl-N-tosyl trichloroacetamide

Amide [176a] has been cyclised previously by a ruthenium-catalysed cyclisation.[28] It was found that δ-lactam [178a] was formed as a by-product (ratio [177a] : [178a] = 23:17). This was due to the steric hindrance of the methyl group on the alkene of amide [176a] (Scheme 5.6). A mixture of γ-lactam [177a] and δ–lactam [178a] was reported in 23% and 17% yield respectively.



Scheme 5.6

We were interested in repeating the reaction but using the CuCl-[164] catalyst system. Hence, 30mol% of CuCl-[164] catalyst was used and the cyclisation of N-unsubstituted [176a] was carried out in refluxing toluene solution for 24 hours. Unfortunately, no product was formed with only starting amide [176a] being isolated. However, cyclisation of the N-tosyl protected amide [176b] was rapid and was

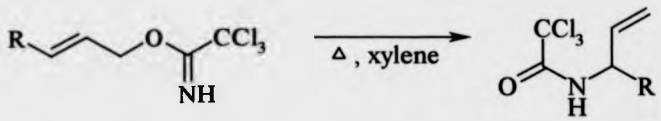
complete after only 20 minutes. Contrary to the previously reported Ru mediated reaction, only the γ-lactam [177b] was detected as a single product in 88% yield. No δ-lactam [178b] was found. The original Ru catalysed cyclisation was conducted at elevated temperature and consequently we heated the reaction at reflux in toluene solution for 24 hours in order to investigate the effect of reaction temperature on the regiochemistry of the cyclisation. At this high temperature, we still found that the γ-lactam [177b] was the only product however the yield dropped to 69%. In conclusion, the cyclisation of amide [176b] with CuCl-[164] catalyst gave the desired γ-lactam as a single product. The steric hindrance of methyl group in [173b] did not affect the regioselectivity of the cyclisations as it did for the ruthenium mediate reaction but did affect the yield.

5.5 Stereoselectivity of 1-buten-3-yl trichloro-acetamide [179] and 3-phenyl-1-propen-3-yl trichloroacetamide [180] cyclisations

5.5.1 preparation of starting amides [179] and [180]

In order to investigate the stereochemistry of CuCl-[164] catalysed cyclisation, amides [179] and [180] were prepared and used as substrates for the cyclisations. These known amides were prepared by thermal allylic rearrangement of allylic

trichloroacetimidic esters [181] and [182] to afford the corresponding trichloroacetamides [179] and [180] (Scheme 5.7).[91] The esters [181] and [182] were easily prepared by condensing the corresponding allylic alcohols with trichloroacetonitrile.

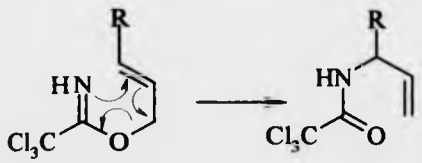


[181] : R = Me
[182] : R = Ph

[179] : R = Me (61%)
[180] : R = Ph (33%)

Scheme 5.7

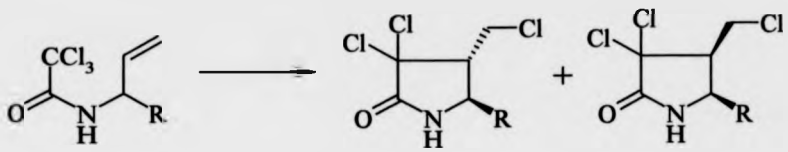
The possible mechanism was 1,3 interchange of allylic esters [181] and [182] as showed in Scheme 5.8.



Scheme 5.8

5.5.2 Cyclisation of amides [179] and [180]

Both amides [179] and [180] were cyclised with 30mol% CuCl-[164] catalyst in refluxing toluene for 24 hours (Scheme 5.9).



[183a] : R = Me [183b] : R = Me
[184a] : R = Ph [184b] : R = Ph

Scheme 5.9

For the cyclisation of [179], it was found that the reaction produced the cyclised products as a mixture of *cis* and *trans* isomers, [183a] and [183b], in a ratio 15 to 85 in 52% overall yield. When R was bigger in [180], the reaction produced the cyclised products as a mixture of *cis* and *trans* isomer (9:91) in 50% yield. The results showed that the cyclisations of amides [179] and [180] provided *trans* isomers as the major products and the stereoselectivities of these amide cyclisations depended upon the size of the R group.

5.5.3 Comparison with published results

The cyclisation of [179] and [180] have been previously published [36] using 1%mole of $RuCl_2(PPh_3)_3$ as a catalyst (in refluxing xylene solution for 1 hour). The results are shown as a comparison in table 5.1.

Entry	Compound	R	1%mole of $RuCl_2(PPh_3)_3$		30%mole of CuCl-[164]	
			Yield(%)	*cis* : *trans*	Yield(%)	*cis* : *trans*
1	[179]	Me	64	16 : 84	52	15 : 85
2	[180]	Ph	60	0 : 100	50	9 : 91

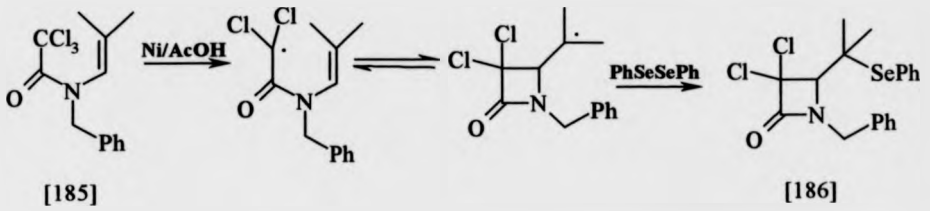
Table 5.1 the resulted comparison between $RuCl_2(PPh_3)_3$ and CuCl-[164]

It can be seen that the $RuCl_2(PPh_3)_3$ catalysed cyclisations gave slightly better yields in both the methyl and the phenyl series. In addition, the *cis* and *trans* selectivities between the $RuCl_2(PPh_3)_3$ and CuCl-[164] cyclisations were similar (16:84 and 15 : 85, 0 : 100 and 9 : 91). In conclusion, the stereochemical results did not vary much by the catalysts used. More importantly, however the different catalyst systems did affect the rate of cyclisation.

5.6. Investigation of intermolecular capture of the cyclised radicals

In the chlorine atom transfer cyclisation, chlorine atom will be transferred from $Cu(II)Cl_2$ to the cyclised radical intermediate. We were consequently interested in the intermolecular capture of the radicals by other radicophilic reagents. A literature survey showed that diphenyl diselenide and ethyl cyanoformate could be used as the radicophilic reagents in Ni^0 mediated atom transfer cyclisations.[92] They reported the

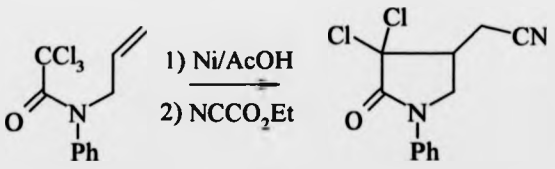
formation of [186] when the enamide [185] was treated with 2 equivalents of diphenyl diselenide in a nickel powder/acetic acid mediated radical cyclisation (Scheme 5.10).



[185] [186]

Scheme 5.10

Interestingly, no β-lactam was produced when the diselenide trap was omitted.[92b] Similarly to diphenyl diselenide, ethyl cyanoformate was used as a source of the cyano group which was transferred to the cyclised radical of the amide [186] to afford the lactam [187] (Scheme 5.11).[92a]

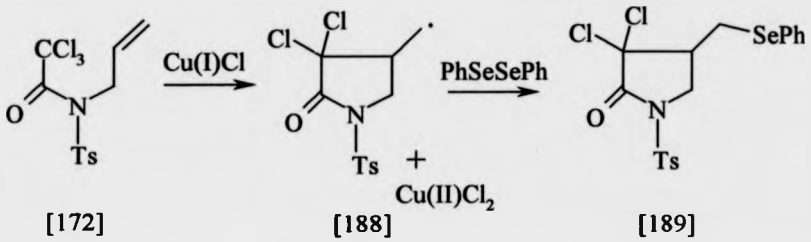


[186] [187]

Scheme 5.11

In order to determine if our atom transfer procedure would allow for intermolecular capture of the cyclised radical, we attempted reactions in the presence of both diphenyl diselenide (PhSeSePh) and ethyl cyanoformate ($NCCO_2Et$). Firstly, the

cyclisation of the trichloroacetamide [172] was carried out in toluene solution with 30%mole of CuCl-[164] and 3 equivalents of PhSeSePh. The reaction was stirred at room temperature for 2 hours. It was found that after this time the conversion of amide [172] to lactam [189] was only 24% (Scheme 5.12).



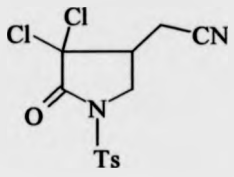
[172] [188] [189]

Scheme 5.12

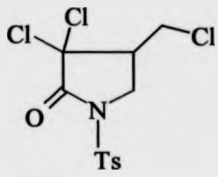
The reaction was allowed to continue for a longer period (72 hours) however no increase in the conversion of [172] had occurred. Satisfyingly, the cyclised radical intermediate [188] was trapped with PhSeSePh to afford the cyclised product [189]. The low yield can be easily explained by the fact that chloride atom transfer to the cyclised radical [188] from $CuCl_2$ could not occur. Thus the CuCl active catalyst could not be regenerated. The reaction could only proceed in a stoichiometric fashion. In order to prove this explanation, the reaction was then carried out with 1 equivalent of Cu(I)Cl-[164] to the starting amide [172] using the same conditions. It was found that the lactam [189] was isolated in a higher yield (65%).

In an attempt to introduce a CN group into the product, the reaction was repeated in the presence of 10 equivalents of ethyl cyanoformate. Interestingly, no lactam [190]

was produced in the reaction. The isolated γ-lactam [173] was collected instead in 71% yield.



[190]

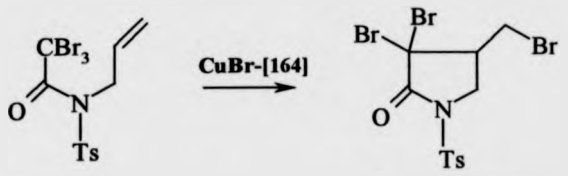


[173]

This result indicated that the competition between transferring the cyano group and chloride atom was in favour of the latter process.

5.7. Copper(I) bromide catalysed cyclisations.

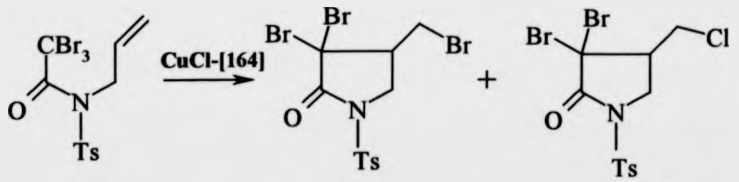
We were also interested in investigating whether other halogens would undergo atom transfer cyclisation. Consequently, tribromoactamide [191] was prepared in the same manner as for the trichloroacetamide [172] instead tribromoacetyl chloride was used as acylating agent. The cyclisation of the amide [191] was carried out with the presence of copper(I)bromide-[164] as the catalyst system in toluene solution for 30 minutes at room temperature (Scheme 5.13). From this first attempt, we found that the cyclisation afforded a γ-lactam [192] in 87% yield.



[191] [192]

Scheme 5.13

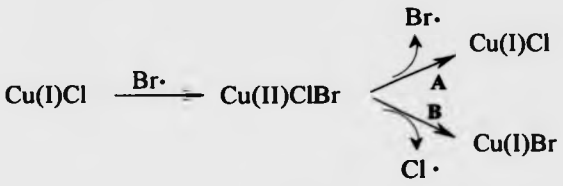
The result showed that copper(I) chloride may be replaced by copper(I) bromide in the reaction of halogen atom-transfer cyclisation. Consequently, the amide [191] was treated with CuCl instead of CuBr in order to determine which of the halogen atoms would be transferred in preference (Scheme 5.14).



[191] [192] [193]

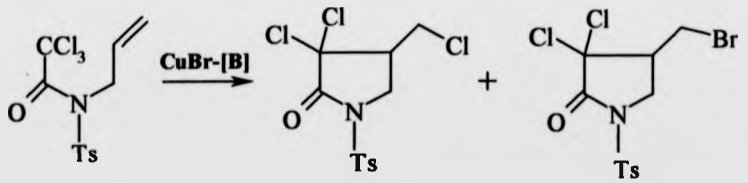
Scheme 5.14

It was found that when 30 mol% of CuCl [164] was used the cyclisation furnished lactam [192] and [193] in a ratio of 96 : 4. When 1 equivalent of CuCl-[164] was used, the ratio of [192] and [193] was found to be 92:8 which was not significantly changed. From these results, we could determine that the bromine atom transferred from the mixed halide Cu(II)ClBr-[164] complex more rapidly than the chlorine atom. The possible mechanism may be explained as Scheme 5.15



Scheme 5.15

We can see that Br radical from amide [191] could transfer to copper(I) complex to give Cu(II)ClBr. Therefore, there were two possible ways of transferring halogen atom back to the cyclised radical intermediate, A and B. In pathway A, a Br radical was transferred to give Cu(I)Cl whereas pathway B would give Cu(I)Br. The result showed that lactam [192] was the major product which was corresponding with the transferring of the Br atom *via* pathway A. In order to prove that Br atom transfer in pathway A was more favoured than Cl atom transferring in pathway B, CuBr was used in the cyclisation of [172] (Scheme 5.16). In the cyclisation the same intermediate Cu(II)ClBr complex would be formed and we would thus expect to get selective Br radical transfer as observed previously.



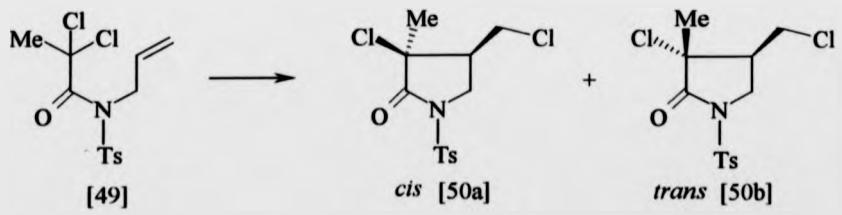
[172] [173] [194]

Scheme 5.16

However, this cyclisation gave lactam [173] and [194] in ratio 83:17 when 30mol% of catalyst was used which increased to 70:30 with 1 equivalent of catalyst. Consequently in this case the chlorine atom was selectively transferred. The reason for this interesting unexpected result remains unclear.

5.8 Cyclisation of N-allyl-N-tosyl dichloromethyl-acetamide [49]

The cyclisation of [49] has been reported earlier by Slough and co-worker in 1993.[37] A ruthenium (II) complex was used as the catalyst system. The cyclisation was carried out at 100 °C for 4 hours to provide the mixture of diastereomers [50a] and [50b] in 69% yield including some unreacted starting amide [49]. The diastereomeric ratio of the *cis* to *trans* isomer was reported to be 27:73 (Scheme 5.17).



Scheme 5.17

This work prompted us to investigate the cyclisation of amide [49] in the presence of our copper (I) complex. The effects of both solvent and equivalent of ligand [164] on the diastereoselectivity of the amide [49] cyclisation were studied. Moreover, we monitored how the rate of cyclisation was altered when different ligand analogues were used.

5.8.1 Initial investigation

Initially, the effect of both solvent and the equivalents of ligand [164] used on the diastereoselectivity of the amide [49] cyclisation was investigated. Imine [164] was used as a ligand to form the copper complex with 30mol% of CuCl. The amide [49] underwent cyclisation at room temperature for 24 hours in either toluene or dichloromethane solution and the diastereomeric ratios were determined by ^{1}H NMR in $CDCl_3$ solution. The *cis*-proton chemical shift of C*H*CCl_2 appeared as a multiplet further downfield (2.88 ppm) than of *trans* C*H*CCl_2 proton (2.60 ppm). The integration of these protons was used to measure the isomeric ratios. The results of the cyclisations are shown in table 5.2.

Entry	Solvent	Ligand concentration (%mole)	Yield (%)	d.e. (%)
1	CH_2Cl_2	30	97	26
2	CH_2Cl_2	60	99	30
3	Toluene	30	90	46
4	Toluene	60	93	32

Table 5.2 Cyclisation of N-allyl-N-tosyl dichloromethylacetamide [49] in toluene and dichloromethane solution

It was found that the cyclisations of amide [49] with CuCl-[164] catalysed system gave the cyclised products in 90-99% yield. The *trans* isomer was found as a major product with 26-46 %d.e. In dichloromethane solution the cyclisation gave a slightly better yield than in toluene solution. In addition, when the amount of ligand was increased from 30 to 60 mol%, the yield was also slightly increased in both solvents. The diastereoselectivity was similar in all runs with the use of 30mol% ligand in toluene giving the highest selection.

5.8.2 Rate of the cyclisation

5.8.2.1 Introduction

As mentioned earlier, Cu(I)Cl-(ligand) complex acts as a halogen carrier. The initial atom transfer may be described by the equilibrium of Cu(I)Cl and $Cu(II)Cl_2$ as shown in equation 5.1.[67] This reaction is likely to be the rate limiting step in all the cyclisation reactions reported in this thesis. The rate will therefore be determined by the position of this equilibrium (i.e. redox potential of Cu(I) /Cu(II) complex).

$$R{-}Cl + Cu(I)Cl \underset{}{\overset{k}{\rightleftharpoons}} R\cdot + Cu(II)Cl_2$$

Equation 5.1

We can alter the redox potential by changing the nature of the ligand. Consequently, we were interested in investigation how ligand structure effected the equilibrium. The

effects of ligand concentration and of ligand structure were studied on the substrate [49]. This was chosen since the time of the reaction to go completion at room temperature was not too rapid allowing us to easily follow the course of the reaction by NMR.

Assuming a pseudo first order rate law:

$$\ln \frac{[A]}{[A]_o} = -kt$$

[A] = concentration of substrate A

$[A]_o$ = concentration of substrate A at t = 0

t = time

k = rate constant

Consequently $\ln[A]/[A]_o$ is plotted against *t*, a first-order reaction will give a straight line and k may be obtained from the gradient. We could then measure the effect of the change on k by ligand analogues.

5.8.2.2 Effect of ligand concentration

Initially, a 0.112M solution of the starting amide [49] in dichloromethane in the presence of 30 mol% of CuCl was used. Aliquots were collected every hour for 5 hours. The conversion of starting amide [49] in each fraction was determined by ^1H NMR. The graph below illustrates the effect on the rate of varying amounts of added ligand.

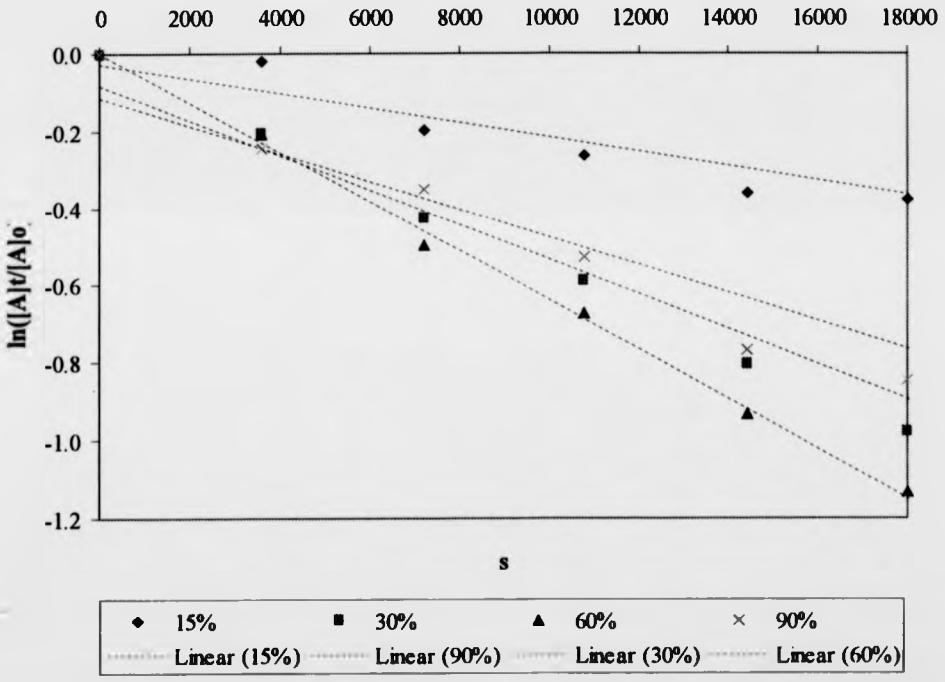


Figure 5.1 ln[A]/[A]o against time of the amide [49] cyclisation with 15, 30, 60 and 90mol% of ligand [164]

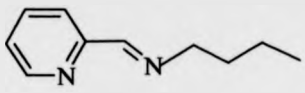
Entry	Ligand concentration (%mole)	k ($M^{-1}s^{-1}$)
1	15	2×10^{-5}
2	30	5×10^{-5}
3	60	6×10^{-5}
4	90	4×10^{-5}

Table 5.3 k of the amide [49] cyclisation with 15, 30, 60 and 90 mol% of ligand [164]

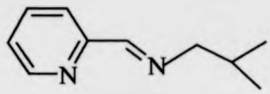
The results indicated that the cyclisation is slowest when only 15 mol% of ligand [164] was used (ie 0.5/1 of ligand/Cu(I)Cl ratio) but that 60 mol% of ligand [164] was optimal. However the overall rate changes were marginal. No advantage was found in adding, more than 60 mol% of ligand (i.e. 2/1 of ligand/Cu(I)Cl ration), indicating that the optimum complex contains a 2:1 ligand/Cu(I)Cl ratio.

5.8.2.3 Effect of ligand structure

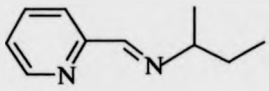
Since the results from the last section indicated optimum catalysis occurred when 60 mol% of ligand [164] was used with 30%mole of CuCl, we screened a range of sterically modified ligands under these conditions [195]-[199]. These ligands have the same basic structure as ligand [164] which contains a N-pentyl group. The ligands were easily prepared using commercial amines and 2-pyridine carbaldehyde. In order to determine the effect on the rate of the steric nature of the N-substituent, we prepared the *n* butyl, *i*-butyl, *s*-butyl and *t*-butyl analogues.



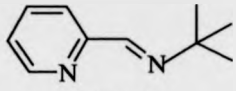
[195]



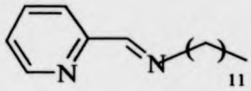
[196]



[197]

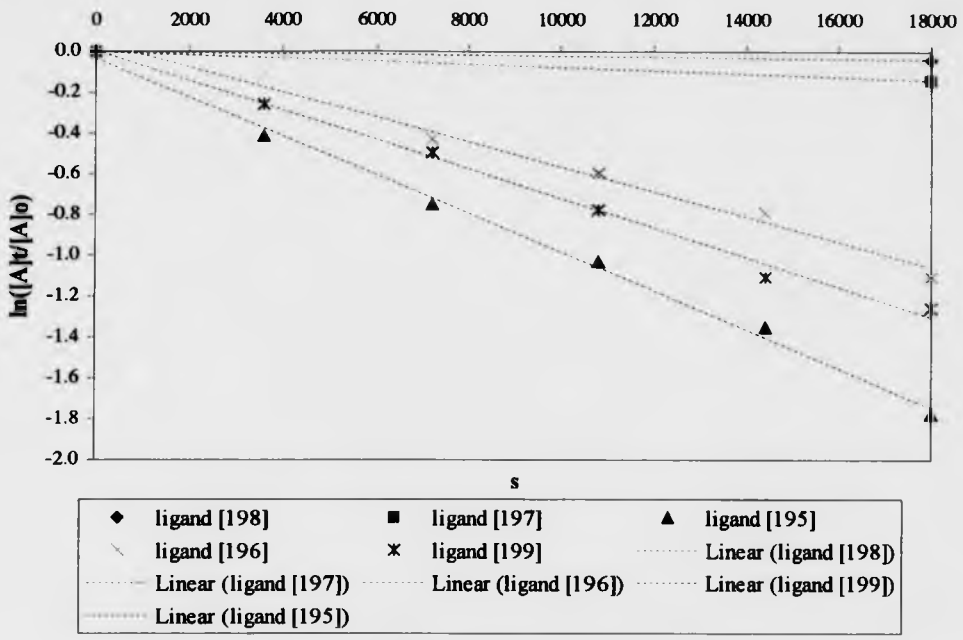


[198]



[199]

The n-butyl group in ligand [195] represents a small primary alkyl group whereas the dodecyl group in ligand [199] was chosen as a longer chain primary group. Similarly, iso-butyl group in ligand [196] was chosen to present as a bulky primary group whereas secondary and tertiary alkyl groups were represented by *iso*-butyl and *tert*-butyl in ligand [197] and [198] respectively. ln $[A]/[A]_o$ of each cyclisation was plotted against time as shown in Figure 5.2 and k of the reaction was provided from slope of each line is shown in Table 5.4.



***Note**: For the cyclisations with ligand [197] and [198], the samples were collected at 5, 24 and 48 hours and ln[A]/[A]o was plotted against those time.*

Figure 5.2. ln $[A]/[A]_o$ against time of the amide cyclisation with ligand [195]-[199].

Entry	Ligand	k ($M^{-1}s^{-1}$)
1	[195]	9×10^{-5}
2	[196]	6×10^{-5}
3	[197]	6×10^{-6}
4	[198]	3×10^{-6}
5	[199]	7×10^{-5}

Table 5.4. k of the amide [49] cyclisation with ligand [195]-[199].

It was found that the cyclisations with ligand that contained primary alkyl groups (eg, [194], [195], and [198]) were faster than those cyclisations with ligands that contained more sterically hindered groups such as the secondary or tertiary group in ligands [196] and [197]. Ligand [194] mediated the fastest cyclisation and this indicated that the shorter primary chain gave the best results with the more bulky group retarding the rate.

5.8.2.4 Effect of solvent

The effect of solvent on the rate of reaction was also studied. In these experiments, 30 and 60 mol% of ligand [164] were used using the same conditions as in the previous work. The results are shown in Figure 5.3 and Table 5.5.

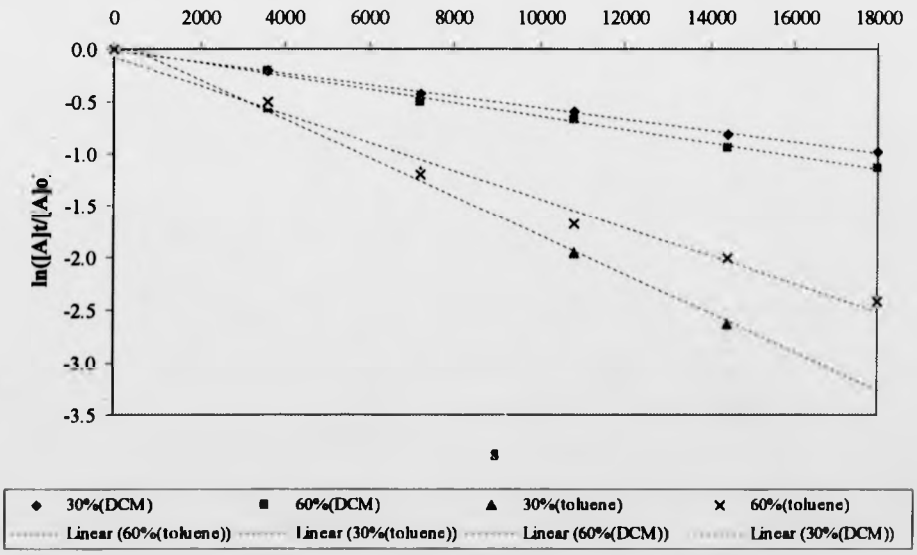
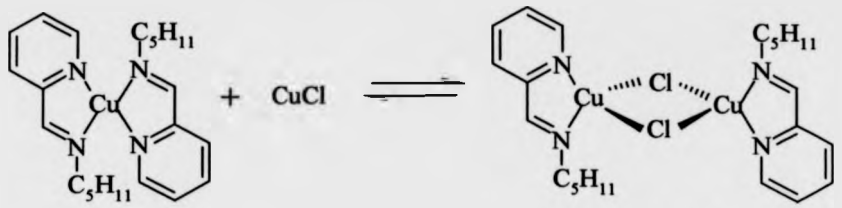


Figure 5.3. ln $[A]/[A]_o$ against time of amide [49] cyclisation with 30% and 60% mole of ligand [164] in toluene and dichloromethane solution.

Entry	Ligand concentration (%mole)	Solvent	k ($M^{-1}s^{-1}$)
1	30	CH_2Cl_2	5×10^{-5}
2	60	CH_2Cl_2	6×10^{-5}
3	30	Toluene	2×10^{-4}
4	60	Toluene	1×10^{-4}

Table 5.5. k of the amide [49] cyclisation with 30% and 60% mole of ligand [164] in toluene and dichloromethane solution.

It was found that the cyclisations in toluene solution with both 30 and 60 mol% of ligand were more rapid than those conducted in dichloromethane. In fact using 30 mol% of ligand in toluene (entry 3), the reaction was completed in less than 5 hours. The results indicate that rate constants in toluene solution are about ten times as fast as in dichloromethane solution. This may be due to either a solubility factor or by the solvent effecting the Cu(I)/Cu(II) redox potential. Interestingly, whereas our previous studies indicated that a 2:1 of ligand/Cu(I)Cl complex was optimal in dichloromethane solution this work indicated that in toluene solution a 1:1 complex was preferred. There are various possible structures of the active catalyst in solution for example the tetrahedral Cu(I) complex [166] may be in equilibrium with the dimer [167] (Scheme 5.18). The active catalyst may be one or both of these complexes. The equilibrium may be altered by the solvent and thus this could explain why different levels of added ligand give different results in different solvents.

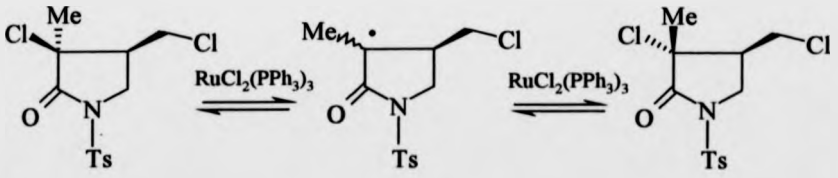


[166] [167]

Scheme 5.18

Thus in toluene [167] might be favoured with 1 equivalent of ligand and this may be the active catalyst however in dichloromethane this dimeric structure might be supressed by formation of loosly co-ordinating solution complexes

5.8.3.Effects on stereochemistry of cyclisation using different ligands



Scheme 5.19

Weinreb has reported that α-chlorine abstraction accounted for diastereomeric equilibration in his study on exocyclic α-chloro esters.[93] In 1993 Slough published

the thermodynamic behaviour of both diastereomers of N-tosyl-2-pyrrolidinones in the presence of a ruthenium catalyst (Scheme 5.19).[34] The reverse rate constants for the equilibrium is reported in Table 5.6. In the above reaction both Weinreb and Slough have indicated that the diastereomers may interconvert under Cu and Ru mediated atom transfer reactions respectively.

Entry	Starting Diastereomeric isomer	k_1 k_{-1} ($\times 10^{-3}$ $M^{-1}s^{-1}$)	Half-life to equilibrium (h)	d.e.(%)
1	*cis*	24.8 + 1.2	2.6	60
		6.5 + 0.3		
2	*trans*	6.5 + 0.5	2.6	62
		24.4 + 1.9		

Table 5.6. Rate constants for N-tosyl 2- pyrrolidinone diastereomers[34]

At the equilibrium (under thermodynamic conditions), the diastereomeric excess is about 60% with a half-life to equilibrium of about 2.6 hours at 100 °C. From our work, we found that Cl atom transfer of the amide [49] in toluene solution at room temperature was faster than in dichloromethane solution. This may explain the better diastereomer excess found in toluene solution than in dichloromethane. The catalyst in toluene solution being more active than in dichloromethane results in a ratio of products closer to the expected thermodynamic ratio. In order to measure the effect of ligand structure on the diastereoselectivity of the reaction of [49] we examined the reaction using the previously prepared ligands [195]-[199]. The reactions were then monitored for 48 hours and the diastereomer excesses were compared at that time as shown in table 5.7.

Entry	Ligand	Ligand concentration(%mole)	Solvent	d.e.(%)
1	[164]	30	toluene	66
2	[164]	60	toluene	54
3	[164]	15	CH_2Cl_2	20
4	[164]	30	CH_2Cl_2	30
5	[164]	60	CH_2Cl_2	50
6	[164]	90	CH_2Cl_2	40
7	[195]	60	CH_2Cl_2	62
8	[196]	60	CH_2Cl_2	42
9	[197]	60	CH_2Cl_2	34
10	[198]	60	CH_2Cl_2	2*
11	[199]	60	CH_2Cl_2	62

** % d.e. of major cis isomer*

Table 5.7 The diastereomer excess of cyclised conditions at 48 hour.

Most of the reactions provided the *trans* isomer as the major product. Table 5.6 shows that the diastereomer excess was dependent on the ligand structure and its concentration. As found before, the best concentration of ligand [164] in toluene solution was 30 mol% while for dichloromethane solution, it was 60 mol%. With less active catalysts containing bulky N-alkyl groups the diastereomer excess was decreased. A long chain-primary alkyl substituent on the ligand [199] gave a similar de% to that of a shorter primary alkyl group [195]. Interestingly, ligand [198] with the very bulky *tert*-butyl substituent provided the *cis* isomer as the major product albeit in 2% de. Hence, kinetically the reactions are likely to furnish the *cis* product but thermodynamically the *trans* product is formed. In order to obtain the true thermodynamic ratio, one of the reactions (Entry 11) was continued for 18 days and provided a good diastereomer excess of 74%.

5.8.4.Conclusion

The cyclisation of N-allyl-N-tosyl dichloromethylacetamide [49] provided the cyclised product [50] in a very good yield (> 90%) using the CuCl-[164] catalyst in both toluene and dichloromethane solution. The cyclisation afforded the *trans* isomer as a major product. The use of two equivalents of ligand [164] gave a faster rate in dichloromethane solution whereas one equivalent of ligand [164] gave the faster rate in toluene solution. The amide underwent cyclisation faster in toluene solution than in dichloromethane solution (as much as ten times). This may be a solubility effect or due to the formation of different "active" catalysts. The steric structure of the ligand affected both the rate and diastereoselectivity of the cyclisation. Ligands with a more bulky structure gave slower cyclisations and smaller diastereomer excesses. Interestingly, with very hindered ligands the cyclisation provided the *cis* isomer as a major product in a very small diastereomer excess (2 % d.e.) after 48 hour.

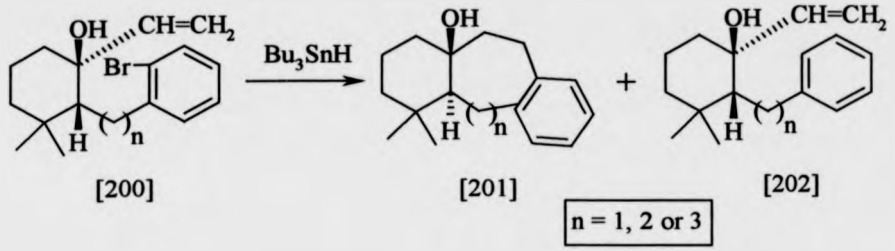
CHAPTER 6

Medium-size lactam synthesis

6.1. Introduction

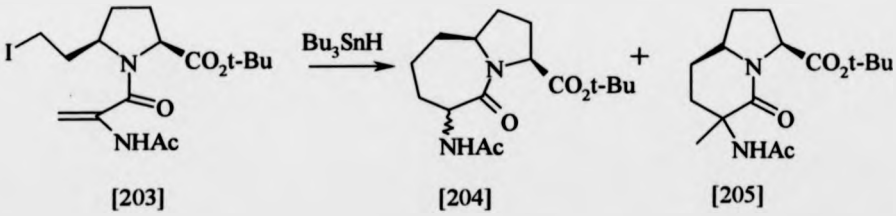
The synthesis of 5-membered lactone and lactam functionality from allyl trichloroacetate and amides using copper catalysts have been reported in chapter 4 and chapter 5 respectively. We were consequently interested in the application of this method for the formation of larger ring lactams (8-, 9- and 11-membered ring systems) since the synthesis of medium-size lactones and lactams has recently received considerable attention by research community and pharmaceutical companies.[94,95]

Synthesis of medium ring by Bu_3SnH mediate radical cyclisation is well documented.[96,97] Ghatak and co-workers have published the application of 7-endo, 8-endo- and 9-endo aryl radical cyclisation of allyl cyclohexanols [200] with tri-n-butyltin hydride. The reactions provided the corresponding tricyclic alcohol [201] (through radical attack at the terminal olefinic carbon centre) in good yields (55-60%).[96] The debrominated olefinic alcohol [202] was also found as a reduced product in 18-20% yield (Scheme 6.1).



Scheme 6.1

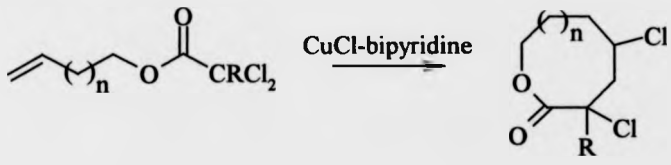
For the example of medium-size lactam cyclisation, Colombo and co-workers have established the synthesis of 7,5-fused bicyclic lactams [204] by radical cyclisation.[98] They reported that the radical cyclisation of pyrrolidinyl precursor [203] *via* the tin hydride method afforded two regioisomeric products, [204] and [205] (Scheme 6.2).



Scheme 6.2

The cyclisation showed very high diastereoselectivity in product [204] (>95%). It was shown that the 7-*endo*-trig and 6-*exo*-trig paths were both favoured processes. It has been reported previously that the simple 6-heptenyl radical cyclises preferentially in the 6-*exo* mode.[65,66] In this case, the reaction follows a 7-*endo* pathway which was explained by the stabilisation exerted through the capto-dative effect.[98]

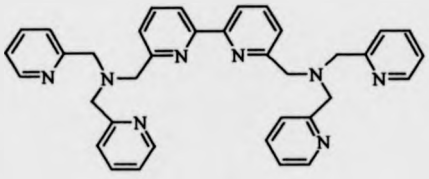
Recently, medium-size ring closures *via* atom transfer radical cyclisation were reported by Speckamp[99] and Verlhac.[100] Speckamp and co-workers published the synthesis of lactones (8- to 12-membered ring systems) in 1994.[99] They reported that the 8- and 9-membered lactones were formed efficiently from alkenyl di- and trichloroacetates by the CuCl-bipyridine catalyst. The acetates underwent cyclisation at high temperature, between 80-190 °C, in 1,2 dichloromethane or benzene solution (Scheme 6.3).



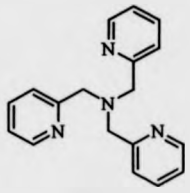
Scheme 6.3

It was found that the cyclisation of acetate,n=2, provided the corresponding lactone in an excellent yield (>92%). When n =3, the yield was decreased giving the desired lactone in only 50% yield. With the short alkenyl chain (n=1), the cyclisation failed completely with only telomerised products being detected. This might be because of the unwillingness of the ester group to adopt the s-*trans*-conformation during the cyclisation reaction. Similarly, only telomerised products were formed in the reaction of acetates, n= 4 and 8. It was assumed that unfavourable entropy effects were more important when the chain was elongated. Hence, significant amount of telomers were detected in the case of the nine-membered lactone as well.

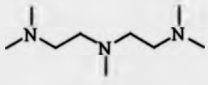
Interestingly, the cyclisation to these lactones was reported recently by Verlhac and co-workers in 1998.[100] They used the new copper and iron complexes formed from ligands [206]-[208]. They found that with these new ligands, the acetates (n=2, 3 and 4) could undergo cyclisation to give the corresponding lactones in good yield (53-99%). In all experiments, no significant amount of telomers could be detected. No work in the formation of medium sized ring lactams *via* atom transfer cyclisation has appeared in the literature.



[206]

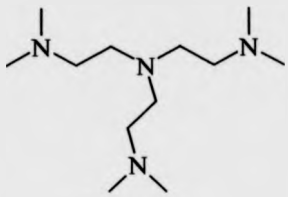


[207]



[208]

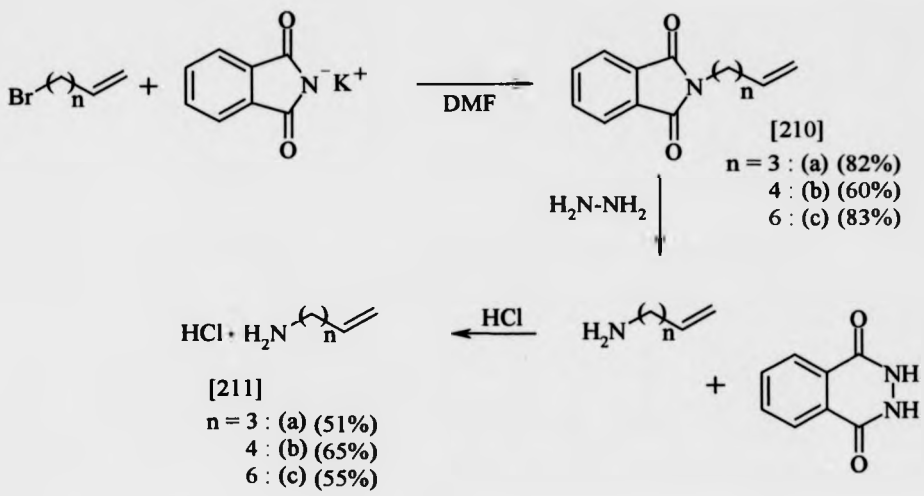
This last work prompted us to investigate medium-size ring lactam formation by the radical transfer method using our copper complexes as the catalyst system. The ligand, tris[2-(diethylamino)ethyl]amine [209], has recently been prepared and studied in atom transfer radical cyclisation by another member of our group.[101] It can be easily prepared in a one-step synthesis using a literature procedure from commercially available tris-(2-aminoethyl)amine.[102] Therefore, [209] was used as a ligand for the copper complex catalysed system in all following experiments in this chapter



[209]

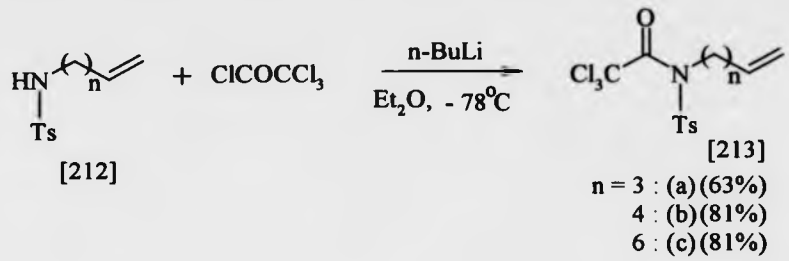
6.2. Preparation of ω-alkenyl trichloroacetamides

Initially, three alkenyl amine hydrochlorides [211a]-[211c] were prepared. The commercial available alkenyl halides were converted to primary amines by the Gabriel synthesis.[103] The halides were treated with potassium phthalimide to produce the alkenyl phthalimides [210a]-[210b] which were heated with hydrazine in an exchange reaction to afford the desired primary amines. The amines were then reacted with HCl to form salts. The salts are less easily oxidised by air than the free bases and it is in this form that the reagents are best preserved and handled (Scheme 6.4).



Scheme 6.4

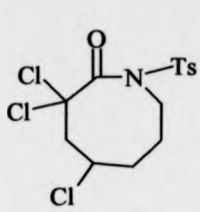
By this method the alkenyl phthalimides [210a]-[210c] were prepared in good yields (60-83%) and primary amines [211a]-[211c] were then furnished in 51-65% yields. The N-tosyl amides [212a]-[212c] were produced by reacting amine hydrochlorides [211a]-[211c] with p-toluenesulphonyl chloride. The amide precursors [213a]-[213c] were finally furnished by reacting N-tosyl amides [212a]-[212c] with trichloroacetyl chloride in diethyl ether at –78 °C for 2 hours (Scheme 6.5). The results showed that the reactions gave the trichloroacetamides [215a]-[215c] in good yields (63-81%). With three amide precursors in hand, we subsequently investigated their cyclisation by using copper-[209] complex as the catalyst system.



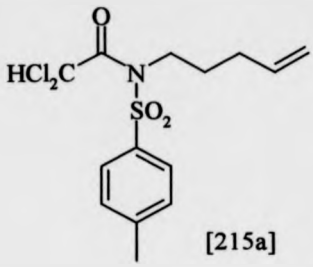
Scheme 6.5

6.3. Initial investigation

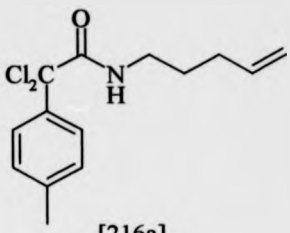
Our first attempt to mediate a cyclisation was the reaction of N-pent-4-enyl-N-tosyl trichloroacetamide [213a] with 30mol% of CuCl-[209]. The reaction was carried out at room temperature in dichloromethane solution, and the reaction was followed by TLC. After 24 hours and TLC still showed starting amide [213a] remained together with new compounds produced from the reaction. The metal complex was then removed by a short silica gel plug and the crude residue was analysed by ^{1}H NMR. The ^{1}H NMR spectra showed that there were 2 new compounds together with starting amide [214a] in ratio 16:31:53 (new product I : new product II : starting amide). Interestingly, there was no expected cyclised product [214a] detected. Further purification by flash column chromatography and further analysis by mass spectroscopy showed that the two new compounds were the reduced product [215a] and the rearranged product [216a] which was collected as the major product.



[214a]

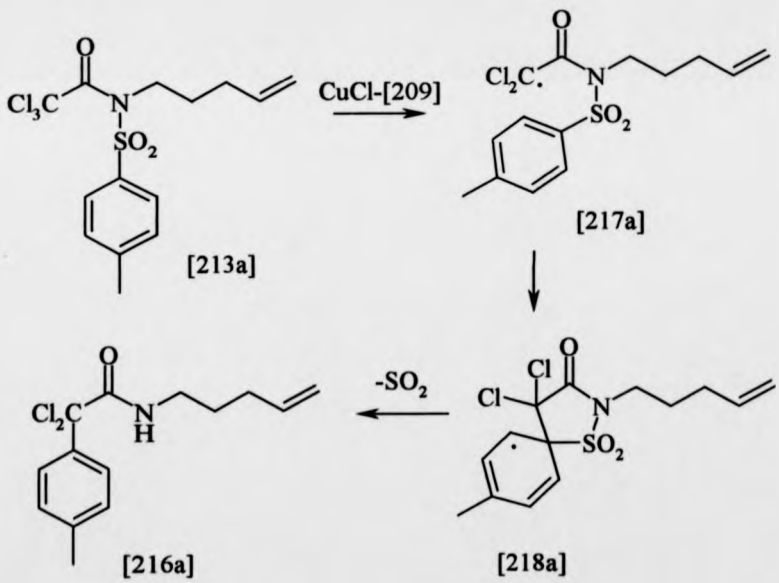


[215a]



[216a]

Spectroscopic analysis of the rearranged compound [216a] indicated that there was no sulfur dioxide in the molecule. It was assumed that the sulfur dioxide was lost in the rearrangement of the aromatic group from the N atom. A possible mechanism is shown in Scheme 6.6.



Scheme 6.6

After initial generation of radical [217a] by conventional atom transfer the desired 8-endo cyclisation is likely to be a relatively slow process and instead a competitive *ipso*-5-exo cyclisation into the aromatic ring can occur to give [218a]. This radical can rearomatise with loss of SO_2 to furnish initially an amidyl radical which undergo by reduction to the observed amide [216a].

A similar mechanism has been previously reported by Speckamp's group and Mothewell's group[104,105] for different substrates and this will be referred to later in section 6.4.1.

The significant amount of reduction product detected is also likely a consequence of the relatively slow 8-endo process. Since there was not any hydrogen donor added to the reaction, the most probable agent responsible for reduction of radical [217a] was either the solvent or the initial radical itself.

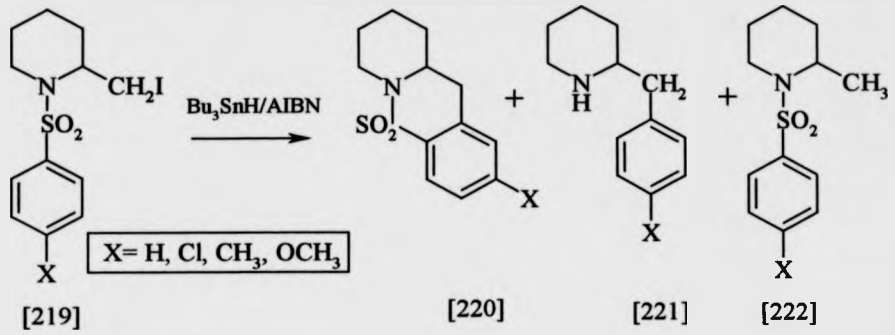
From these initial results it could be concluded that the reaction of the amide [213a] using Cu(I)Cl-[209] was not an efficient catalytic atom transfer process.

6.4. Rearrangement investigation

6.4.1. Introduction

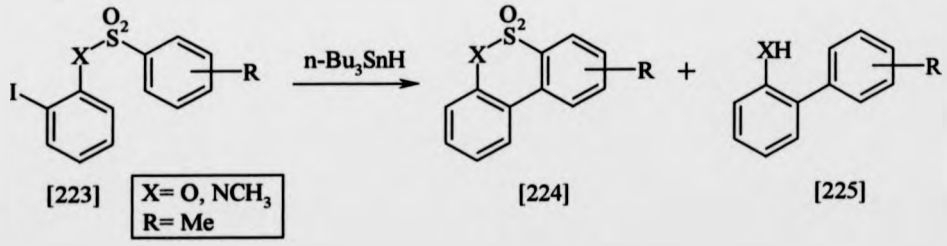
Speckamp and co-workers[104] have reported the reaction of piperidines [219] with Bu_3SnH and AIBN (Scheme 6.7). They found that the reaction gave 3 products which were identified as the addition product [220], the rearranged product [221] and the reduced product [222]. The yields of these compounds were dependant upon the nature of the aryl substituent and the reaction conditions.

It was found that none of the corresponding 1,6-adduct was formed when there was a substituent at the *ortho* position. This could be explained in that steric factors prevented effective hydride transfer by the bulky tin hydride. Substituents at the *para* position did not greatly affect the course of the reaction. The ratio of the three products was also dependent upon temperature. At higher temperatures, the ratio of the rearranged product [221] was higher than at lower temperatures. For example, at 22 °C the ratio of [220]:[221]:[222] was 68:0:30 and the ratio was changed to 26:64:9 at 190°C.



Scheme 6.7

After this work, Motherwell and co-workers[105] studied the synthesis of biaryl compounds of type [225] formed *via* an intramolecular free radical *ipso* substitution of benzylic sulfonates [223]. It was reported that there were two possible products from the reaction, a direct [1,6] addition product [224] as well as the [1,5] *ipso* substitution product [225] (Scheme 6.8).



Scheme 6.8

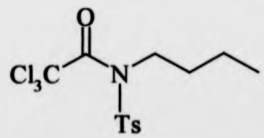
They found that *ipso* substitution was favoured when a methyl substituent was at the *ortho* position. On the other hand, the *ipso* substitution did not take place when the methyl group was substituted at the *para* position. This was due to steric hindrance of

the *ortho*-methyl substituent leading to slow [1,6] addition. Therefore, the [1,6] addition process of *ortho* methyl substituent should be kinetically disfavoured.

The mechanism of [1,5] *ipso* substitution was explained by the rearrangement of the aromatic group by a 1,5 intramolecular radical addition followed by loss of SO_2 and rearomatisation.

6.4.2. Rearrangement of trichloroacetamides

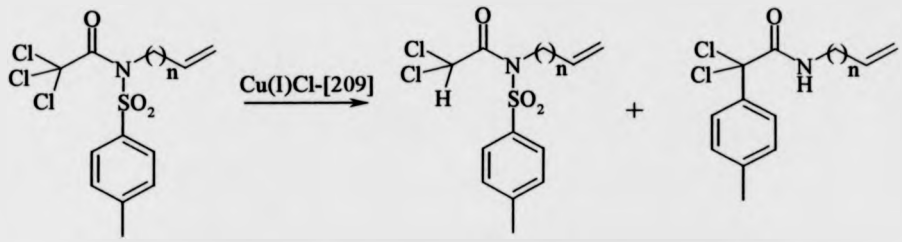
Because our observed the rearrangement was not an atom transfer process, the Cu(I)Cl-[209] complex, in this case, does not act as a catalyst but as an initiator. Therefore, we repeated the reaction with 1 equivalent of Cu(I)Cl-[209] to force the rearrangement reaction to completion. In order to investigate the rearrangement reaction in more detail, we prepared the *n*-butyl precursor [213d] which could not undergo a competing cyclisation. We also examined the reaction of the other substrates [213b] and [213c]



[213d]

The reactions of all the starting amides were carried out at room temperature in dichloromethane solution. After 24 hours, the reaction was quenched and the metal complex was then removed by a short silica gel plug. The ratio of rearranged product

and reduced product were determined from the integrations of the C-1 protons from the ^{1}H-NMR (δ 3.0-4.5 ppm) of the crude residues. The results are shown in table 6.1.



Entry	Compound	Recovered S.M. (%)	Red : Rear
1	[213a]	29	39 : 61
2	[213b]	38	51 : 49
3	[213c]	46	63 : 37
4	[213d]	10	0 :100

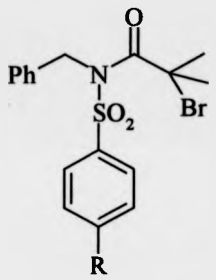
Table 6.1. Reaction of amide [213a]-[213d] with 1 eq. of Cu(I)Cl-[209]

Table 6.1 shows that the ratio of reduced to rearranged products depends upon the length nature of the chain. Interestingly, the reaction of amide [213d] gave only the rearranged compound as a single product with the corresponding reduced product not being detected. The starting amide [213d] was recovered in 10% yield.

The ratio of the two products and the amount of recovered starting amides was dependent on the length of the chain of the N-substituent. As expected, the corresponding cyclised medium-size lactams were not formed. In addition no products arising from direct [1,6] addition were found in these reactions.

6.4.3. Rearrangement of bromoisobutylramides

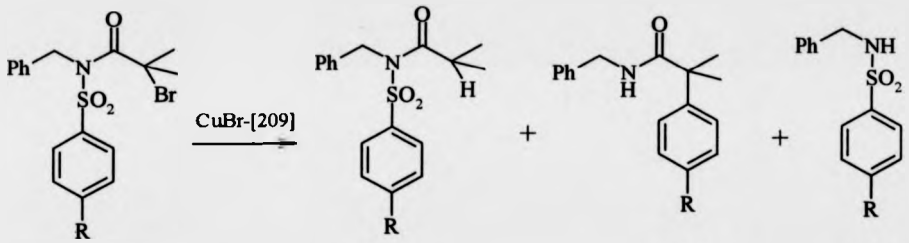
From the previous investigations we discovered that the rearrangement of sulfonyl aromatic groups could take place when tosyl trichloroacetamides were treated with Cu(I)Cl-[209] at room temperature. In order to study the effect of the aromatic *para* substituents on the rearrangement the two precursors, [226a] and [226b], were prepared. These also contained instead of a trichloro initiator the less reaction mono-bromo initiators.



[226] a : R= Me
b : R= H

The new precursors were prepared in the same way as for the other the previous starting amides. Hence, benzylamine was reacted with *p*-totuenesulphonyl chloride and benzenesulfonyl chloride to afford N-benzyltosylamide and N-benzyl benzenesulfonylamide respectively. These sulfonamides were then reacted with bromoisobutyl bromide to furnish the corresponding bromoisobutylramides [226a] and [226b] in 78% and 76% yield respectively.

With these two precursors in hand, we carried the rearrangement reactions using the same conditions as before. In this case, 1 equivalent of Cu(I)Br-[209] was used as the catalyst system. After 24 hours, the reactions were stopped and worked-up and the crude residues were analysed by ^{1}H NMR. Reaction of [226a] furnished two products, the expected rearranged compound [228a] and the N-benzyltosylamide [229a]. The reduced compound [227a] was not found. Similarly, the reaction of amide [226b] also gave the corresponding rearranged product [228b] together with the corresponding cleaved product N-benzyl benzenesulfonylamide [229b]. In addition, however a significant amount of reduced product [227b] was also detected. The results of the two reactions are shown in table 6.2.



[226] a : R= Me
b : R= H

[227] [228] [229]

Entry	Compound	Recovered S.M. (%)	Red : Rear : Clea
1	[226a]	44	0 : 3 : 2
2	[226b]	75	1 : 1 : 1

Table 6.2. Reaction of amide [226a] and [226b] with 1 eq. of Cu(I)Br-[209]

Both reactions provide the corresponding rearranged compounds as well as the corresponding hydrolysis products. The significant amount of reduced product

detected for the benzenesulfonamide [226b] reaction suggests that the rearrangement is relatively slower than for the corresponding N-toluenesulfonamide [226a]. This can be easily explained by considering the stability of the intermediate aromatic radicals.

6.5. Conclusion

The reaction of the long alkenyl chain N-tosylamides with copper(I)-[209] complex furnished reduction and rearrangement products with no cyclisation to form medium ring lactams. The most plausible mechanism to explain the rearrangement is an intramolecular [1,5] *ipso* radical substitution of the starting radical followed by loss of SO_2 and a rearomatisation process. In addition, the intramolecular 1,5 hydrogen abstraction by the initial radicals afforded significant amounts of reduced products. However, direct [1,6] addition products were not formed. The length of the N-alkenyl substituent effected the efficiency of the rearrangement.

CHAPTER 7

Experimental

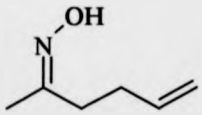
7.1. General experimental

Melting points were recorded on a Stuart Scientific SMP1 melting point apparatus and are uncorrected. Accurate masses were performed either on a Kratos MS80 spectrometer or on MICROMASS AUTOSPEC spectrometer. Only molecular ions (M+ or MH+) and major peaks are reported and the intensities of these peaks are quoted as percentages of the base peak. Microanalyses were recorded at the University of Warwick on a Leeman Labs Inc. CE440 Elemental Analysis. Infar-red spectra were recorded as Nujol mulls or neat or solution, as stated in the text on a Perkin-Elmer 1720x Fourier transform spectrometer, with only selected absorbances (ν_{max}) being reported. ^{1}H NMR spectra were recorded on either 250 MHz, 300 MHz or 400 MHz on a Bruker ACF250, DPX300 or ACP400 instruments respectively. Chemical shifts (δ) are quoted in part per million (ppm) and referenced to the appropriate solvent peak. Coupling constants, J, are quoted in Hertz (Hz). ^{13}C NMR spectra were recorded at 62.5 MHz on a Bruker ACF250, 70 MHz on a Bruker DPX300 and 100 MHz on a Bruker ACP400 instrument. Chemical shifts are quoted in part per million (ppm) and referenced to the appropriate solvent peak. Chemicals used in the experiment were obtained from Sigma-Aldrich, Lancaster, Avocado, Fluka

or Goss at the highest grade available. All solvents were purchased from Fisons Scientific Equipment at SLR grade and purified, when appropriate, by literature method. Anhydrous solvent were obtained thus : acetonitrile and toluene from Sigma-Aldrich; benzene, distilled from sodium under nitrogen; ether, tetrahydrofuran, distilled from sodium-benzophenone ketal under nitrogen. Flash chromatography was carried out on silica gel (Merck Kieselgel $60F_{254}$, 230-400 mesh. TLC was carried out using aluminium backed plates precoated with silica (0.2mm, $60F_{254}$) and were developed using UV fluorescence (245nm), phosphomolybdic acid, potassium permanganate solution or dilute sulphuric acid (in MeOH).

7.2. Experimental for chapter 2

7.2.1. 5-Hexen-2-one oxime [110]

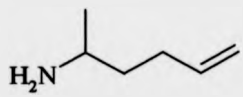


A solution of 5-hexen-2-one (15g, 0.15mol), hydroxylamine hydrochloride (15g, 0.22mol) and pyridine (15ml) in ethanol (150ml) was heated at reflux for one hour. The solvent was removed by evaporation of the hot solution (~65 °C) under reduced pressure. After addition of water (100ml), the oxime was extracted with ether (3x100ml). The combined organic fractions were washed with water, dried over

magnesium sulphate and concentrated under reduced pressure to give the oxime [110] (12.20g, 72%) as light yellow oil. The oxime was used with out further purification. The spectral detail matched those published.[73]

ν_{max}(film)/cm^{-1} 3240 (O-H), 1642 (C=N), 914 (CH=CH_2); δ_H(250MHz, $CDCl_3$) δ: 9.72 (1H, br, s, O***H***), 5.71-5.85 (1H, m, C***H***=CH_2), 4.92-5.07 (2H, m, CH=C***H***$_2$), 2.21-2.44 (4H, m, 2C***H***$_2$,), 1.86 (3H, s, C***H***$_3$); δ_C(62.5MHz, $CDCl_3$) 157.74 (***C***=N), 137.08 (***C***H=CH_2), 115.22 (CH=***C***H$_2$), 35.03, 30.27 (2***C***H$_2$), 13.48 (***C***H$_3$); *m/z* (EI) 113 (M^+, 38%), 96 (68), 82 (52), 55 (87), 42 (100).

7.2.2. 1-Methylpent-4-enylamine [111]



Sodium (10g, 0.43mol, cut in small pieces) was introduced into the refluxing solution of oxime [110] (6g, 53mmol) in ethanol (150ml). As soon as the sodium had completely dissolved, the contents of the flask were cooled and diluted with water (200ml). The flask was then equipped with a condenser and distilled. The distillate was collected in a solution of hydrochloric acid (6M, 30ml) and concentrated under reduced pressure at (~65°C). The crude material was refluxed with potassium hydroxide solution (40%, 25ml) for 1 hour. The mixture was then allowed to cool to room temperature and the organic layer collected and dried. The crude amine [111]

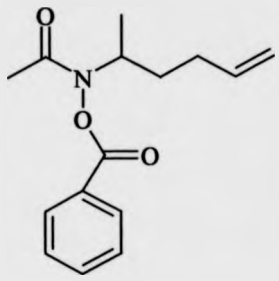
was produced as yellow oil (4.0g, 76%) which was used with out further purification. Spectral details were identical to an authentic sample. [74]

ν_{max}(film)/cm^{-1} 3357 (C-H), 3287 (N-H), 1640 (C=C); δ_H(250MHz, $CDCl_3$) δ: 5.71-5.79 (1H, m, C***H***=CH_2), 4.87-5.02 (2H, m, CH=C***H₂***), 2.80-2.88 (1H, m, C***H***-CH_3), 2.00-2.10 (2H, m, C***H₂***-CH=), 1.33-1.81 (2H, m, -CH-C***H₂***), 1.02 (3H, d, *J*=6.4, C***H₃***); δ_C(62.5MHz, $CDCl_3$) 138.41 (***C***H=CH_2), 114.34 (***C***H=***C***H_2), 46.26 (***C***H-N), 39.00, 30.58 (2***C***H_2), 23.67 (***C***H_3); *m/z* (EI) 99(M^+, 5%), 55 (85), 42 (100).

7.2.3. General procedure for the preparation of N-benzoyloxylamides [108a]-[108g]

A solution of benzoyl peroxide (1 eq.) in dichloromethane was added to 1-methylpent-4-enylamine (1 eq.) and sodium carbonate (4 eq.) in dichloromethane. The mixture was stirred for two hours at room temperature. The acid chloride (1 eq.) then was added dropwise. After stirring for an additional two hours, water was added and the organic layer was separated, washed with water, dried over magnesium sulphate and evaporated under reduced pressure. The crude product was purified by silica gel chromatography.

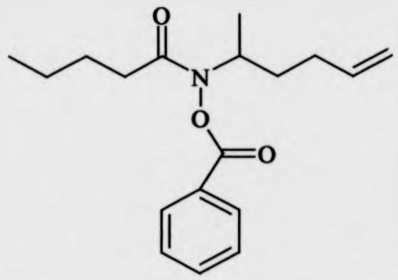
7.2.3.1. N-Benzoyloxy-N-1-methylpent-4-enyl acetamide [108a]



1-Methylpent-4-enylamine (1g, 10mmol) was reacted with acetyl chloride (0.79g, 10mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1). N-Benzoyloxy-N-1-methylpent-4-enyl acetamide [108a] was obtained (1.74g, 66%) as a light yellow oil. (Found MH^+ 262.3205, $C_{15}H_{20}NO_3$ requires 262.3200).

ν_{max}(film)/cm^{-1} 3073,2976, 2933 (C-H), 1765 (OC=O), 1681 (NC=O); δ_H(400MHz, $CDCl_3$) 8.06 (2H, d, 2H, *J*= 7.6, *o*-Ar***H***), 7.64 (1H, t, *J*= 7.6, *p*-Ar***H***), 7.49 (2H, t, *J*= 7.6, *m*-Ar***H***), 5.77 (1H, m, C***H***=CH_2), 4.98 (2H, m, CH=C***H₂***), 4.75 (1H, br, s, C***H***-CH_3), 2.12 (2H, br, m, C***H₂***-CH=), 2.02 (3H, s, OC-C***H₃***), 1.71, 1.52 (2H, br, -CH-C***H₂***), 1.20 (3H, d, *J*=7.1, CH-C***H₃***); δ_C(100MHz, $CDCl_3$) 171.43 (MeC=O), 164.77 (O***C***=O), 137.44 (***C***H=CH_2), 134.19, 129.74, 128.69, 126.53 (4***C*** of Ar), 114.97 (CH=***C***H_2), 52.81 (N-***C***H), 32.78, 30.25 (2***C***H_2), 20.68, (***C***H_3-CO), 17.490 (CH-***C***H_3); ***m/z*** (CI) 262 (M^+ +1, 20%), 220 (10), 184 (100), 105 (70), 84 (57).

7.2.3.2. N-Benzoyloxy-N-1-Methylpent-4-enyl pentamide [108b]



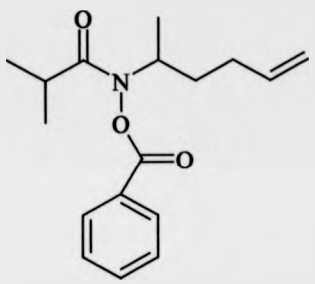
Pentanoic acid (1.5g, 15mmol) was refluxed with excess oxalyl chloride (3g, 24mmole) for one hour. Excess oxalyl chloride was removed on the rotary evaporator and the residue distilled under reduced pressure. Pentanoyl chloride was collected at 80 °C (1.6g, 90%) as a colourless liquid which was used immediately.

1-Methylpent-4-enylamine (0.73g, 7.4mmol) was reacted with pentanoyl chloride (0.89g, 7.4mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave N-benzoyloxy-N-1-Methylpent-4-enyl pentamide [108b] (1.13g, 51%) as a light yellow oil. (Found MH^+ 304.1916, $C_{18}H_{26}NO_3$ requires 304.1913)

ν_{max}(film)/cm^{-1} 3071, 2958, 2932, (C-H), 1765 (OC=O), 1640 (NC=O); δ_H(400MHz, $CDCl_3$) 8.08 (2H, d, *J*= 7.8, *o*-Ar***H***), 7.64 (1H, t, *J*= 7.8, *p*-Ar***H***), 7.44 (2H, t, *J*= 7.8, *m*-Ar***H***), 5.80 (m, 1H, C***H***=CH_2), 5.00 (2H, m, CH=C***H₂***), 4.45 (1H, br, C***H***-CH_3), 2.29 (2H, br, m, C***H₂***-CO), 2.18 (2H, t, *J*= 6.6, C***H₂***-CH=), 1.73, 1.51 (2H, m, -CH-C***H₂***), 1.62 (2H, m, CH_2-C***H₂***-CH_2), 1.31(2H, m, CH_3-C***H₂***-CH_2), 1.19 (3H, d, *J*=6.4

Hz, CH-C***H₃***), 0.86 (3H, t, *J*=7.4, CH_2-C***H₃***); δ_C(100MHz, $CDCl_3$) 166.70 (N***C***=O), 162.86 (O***C***=O), 137.58 (***C***H=CH_2), 134.12, 129.79, 128.69, 126.080 (4***C*** of Ar), 114.89 (CH=***C***H_2), 53.26 (N-***C***H) , 32.92, 30.34 (2***C***H_2 of pentenyl), 29.93, 26.20, 22.14 (3***C***H_2 of pentanyl), 17.82 (CH-***C***H_3), 13.65 (CH_2-***C***H_3); *m/z* (CI) 304 (M^++1, 100%), 262 (46), 220 (22), 184 (43), 105 (93).

7.2.3.3. N-Benzoyloxy-N-1-methylpent-4-enyl-2-methyl-propamide [108c]

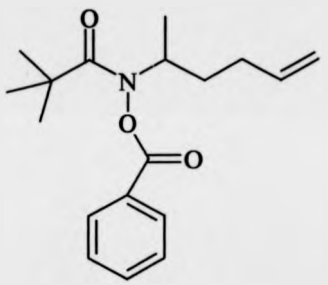


1-Methylpent-4-enylamine (2.0g, 20mmol) was reacted with isobutyryl chloride (2.7g, 20mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave N-benzoyloxy-N-1-methylpent-4-enyl-2-methyl-propamide [108c] (2.97g, 56 %) as a light yellow oil. (Found MH^+ 290.1759, $C_{17}H_{24}NO_3$ requires 290.1756).

ν_{max}(film)/cm^{-1} 3072, 2975, 2934 (C-H), 1765 (OC=O), 1673 (NC=O); δ_H(400MHz, $CDCl_3$) 8.08 (2H, d, *J*= 7.2, *o*-Ar***H***), 7.64 (1H, t, *J*= 7.2, *p*-Ar***H***), 7.14 (2H, t, *J*= 7.2, *m*-Ar***H***), 5.84-5.74 (1H, m, C***H***=CH_2), 4.98 (2H, m, CH=C***H₂***), 4.76 (1H, br, s, C***H***-

N), 2.51-2.62 (1H, m, C*H*-CH_3), 2.14 (2H, br, m, CH_2-CH=), 1.74, 1.52 (2H, br, -CH-CH_2), 1.22 (3H, br, CH_3-CH-N), 1.12 (6H, br, 2CH_3-CH); δ_C(100MHz, $CDCl_3$) 171.52 (NC=O), 165.22 (OC=O), 137.76 (CH=CH_2), 134.33, 129.98, 128.95, 126.96 (4C of Ar), 115.18 (CH=CH_2), 53.39 (N-CH), 33.09 (CH_2) , 31.12 (CH-$(CH_3)_2$), 30.52 (CH_2), 18.79 (2CH_3-CH), 17.75 (CH-CH_3); *m/z* (CI) 290 (M^++1, 10%) 220 (88), 105 (100).

7.2.3.4. N-Benzoyloxy-N-1-methylpent-4-enyl-(2-dimethyl)-propamide [108d]

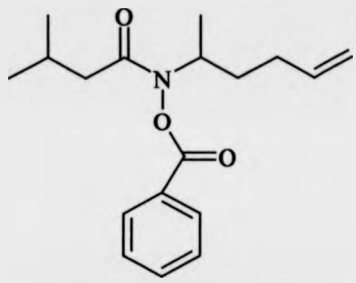


1-Methylpent-4-enylamine (1.9g, 19mmol) was reacted with trimetylacetyl chloride (1.2g, 19mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave N-benzoyloxy-N-1-methylpent-4-enyl-(2-dimethyl)-propamide [108d] (2.25g, 39%) as a light yellow oil. (Found MH^+ 304.1918, $C_{18}H_{26}NO_3$ requires 304.1913).

ν_{max}(film)/cm^{-1} 3073, 2975, 2934 (C-H), 1766 (OC=O), 1660 (NC=O); δ_H(400MHz, $CDCl_3$) 8.08 (2H, d, *J*= 7.5, *o*-Ar*H*), 7.65 (1H, t, *J*= 7.5, *p*-Ar*H*), 7.50 (2H, t, *J*= 7.5,

m-Ar***H***), 5.80 (1H, m, C***H***=CH_2), 4.98 (1H, m, CH=C***H***$_2$), 4.54 (1H, br, C***H***-CH_3), 2.15 (2H, br, m, C***H***$_2$-CH=), 1.84, 1.53 (2H, br, CH-C***H***$_2$), 1.25 (3H, d, *J*=7.10 C***H***$_3$-CH-), 1.21 (9H, s, 3C***H***$_3$-C-); δ_C(100MHz, $CDCl_3$) 162.91 (O***C***=O), 137.74 (***C***H=CH_2), 134.03, 129.78, 128.81, 127.30 (4***C*** of Ar), 114.92 (CH=***C***H$_2$), 99.87 (***C***-CH_3), 32.90, 30.57 (2***C***H$_2$), 27.29 (3***C***H$_3$-C), 17.50 (CH-***C***H$_3$); *m/z* (CI) 304 (M^++1, 47%), 204 (45), 105 (42), 102 (100), 85 (69).

7.2.3.5. N-Benzoyloxy-N-1-methylpent-4-enyl-3-methyl-butamide [108e]

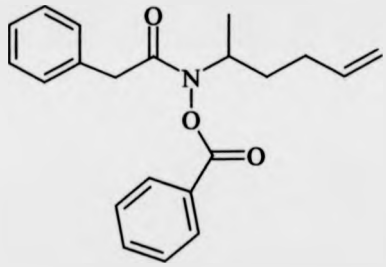


1-Methylpent-4-enylamine (2.0g, 20mmol) was reacted with isovaleryl chloride (2.5g. 20mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave N-benzoyloxy-N-1-methylpent-4-enyl-3-methyl-butamide [108e] (2.50g, 41%) as a light yellow oil. (Found MH+ 304.1919, $C_{18}H_{26}NO_3$ requires 304.1912).

ν_{max}(film)/cm^{-1} 3071, 2960, 2870 (C-H), 1765 (OC=O), 1685 (NC=O); δ_H(400MHz, $CDCl_3$) 8.09 (2H, d, *J*= 7.3, *o*-Ar***H***), 7.66 (1H, t, *J*= 7.3, *p*-Ar***H***), 7.52 (2H, t, *J*= 7.3,

m-Ar*H*), 5.85-5.77 (1H, m, C*H*=CH_2), 5.01 (2H, br, m, CH=CH_2), 4.79 (1H, br, s, C*H*-N), 2.16-2.27 (5H, br, m, CH_2-CH=, CH_2-CO, C*H*-CH_3), 1.74, 1.53 (2H, br, -CH-CH_2-CH), 1.22 (3H, br, CH_3-CH-N), 0.94 (6H, br, 2CH_3-CH); δ_C(100MHz, $CDCl_3$) 170.83 (N*C*=O), 165.00 (O*C*=O), 137.77 (*C*H=CH_2), 134.33, 130.02, 128.92, 126.98 (4*C* of Ar) , 115.23 (CH=*C*H_2), 53.12 (N-*C*H), 41.64 (*C*H-CH_3), 33.10, 30.53 (2*C*H_2), 24.99 (*C*H_2-CO), 22.64 (2*C*H_3-CH), 17.80 (*C*H_3); *m/z* (CI) 304 (M^++1, 85%), 220 (62), 184 (36), 105 (100).

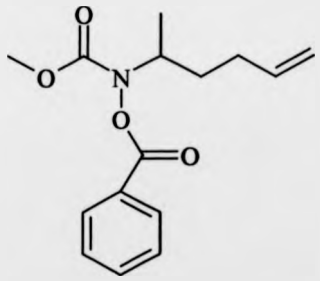
7.2.3.6. N-Benzoyloxy-N-1-methylpent-4-enyl 2-phenyl-acetamide [108f]



1-methylpent-4-enylamine (1.4g, 14mmol) was reacted with phenylacetyl chloride (2.2g, 14mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave N-benzoyloxy-N-1-methylpent-4-enyl 2-phenyl-acetamide [108f] (1.66g, 35%) as a light yellow oil. (Found MH^+ 338.1759, $C_{21}H_{24}NO_3$ requires 338.1756).

ν_{max}(film)/cm^{-1} 3064, 3030, 2976, 2933 (C-H), 1765 (OC=O), 1672 (NC=O); δ_H(400MHz, $CDCl_3$) 8.04 (2H, d, *J*= 7.4, *o*-Ar***H***), 7.66 (1H, t, *J*= 7.4, *p*-Ar***H***), 7.51 (2H, t, *J*= 7.4, ***m***-Ar***H***), 7.19-7.29 (5H, m, C_6H_5-CH_2), 5.76 (1H, m, C***H***=CH_2), 4.92 (2H, m, CH=C***H$_2$***), 4.77 (1H, br, s, C***H***-N), 3.63 (2H, br, s, C***H$_2$***-Ph), 2.09 (2H, br, m, C***H$_2$***-CH=), 1.72, 1.52 (2H, br, -CH-C***H$_2$***), 1.18 (3H, d, *J*=5.2, C***H$_3$***-CH); δ_C(100MHz, $CDCl_3$) 137.74 (***C***H=CH_2), 134.50, 130.11, 129.84, 129.32, 128.92, 128.53, 126.99, 125.66 (8***C*** of 2Ph), 115.22 (CH=***C***H_2), 53.75 (***C***H-N), 40.49 (***C***H_2-Ph), 33.04, 30.44 (2***C***H_2), 17.68 (***C***H_3); *m/z* (CI) 338 (M^++1, 20%), 218 (33), 122 (30), 105 (100).

7.2.3.7. N-Benzoyloxy-1-methylpent-4-enyl-methoxycarbamate [108g]

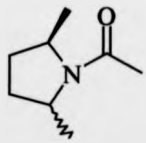


1-Methylpent-4-enylamine (1.5g, 15mmol) was reacted with methylchloro formate (1.4g, 15mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave N-benzoyloxy-1-methylpent-4-enyl-methoxycarbamate [108g] (2.38g, 57%) as a light yellow oil. (Found MH+. 278.1399, $C_{15}H_{20}NO_4$ requires 278.1392).

ν_{max}(film)/cm^{-1} 3072, 2976, 2934 (C-H), 1772 (OC=O), 1719 (NC=O); δ_H(400MHz, $CDCl_3$) 8.06 (2H, d, *J*= 7.8, *o*-Ar***H***), 7.60 (1H, t, *J*= 7.8, *p*-Ar***H***), 7.46 (2H, t, *J*= 7.8, *m*-Ar***H***), 5.78 (1H, m, C***H***=CH_2), 5.00 (2H, m, CH=C***H$_2$***), 4.67 (1H, br, s, C***H***-N), 3.75 (3H, s, C***H$_3$***-O), 2.17 (2H, br, m, C***H$_2$***-CH=), 1.74, 1.53 (2H, br, -CH-C***H$_2$***), 1.24 (3H, br, C***H$_3$***-CH); δ_C(100MHz, $CDCl_3$) 170.94 (N***C***=O), 164.45 (O***C***=O), 137.74 (***C***H=CH_2), 133.92, 124.95, 128.72, 127.44 (4***C*** of Ar), 115.20 (CH=***C***H_2), 55.81 (O***C***H_3), 53.81 (N-***C***H), 32.94, 30.44 (2***C***H_2), 17.58 (***C***H_3); *m/z* (CI) 278 (M^++1, 25%), 105 (100), 98 (94).

7.2.4. Amidyl radical cyclisations.

7.2.4.1. N-Acetyl-2,5-dimethylpyrrolidine [116a] and [117a]

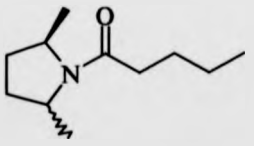


A solution of tributyltin hydride (183mg, 0.63mmol, 1.2 eq.) and AIBN (9.2mg, 0.06mmol, 0.1 eq.) in a deoxygenated mixture of cyclohexane (2.5 ml) and toluene (2.5 ml) was added dropwise over 7 hours to a refluxing solution of acetic acid benzoyloxy-1-methylpent-4-enyl amide [107a] (130mg, 0.5mmol, 1eq.) in deoxygenated cyclohexane (5ml). After addition, the reaction was refluxed further for 12 hours. A further solution of tributyltin hydride (91.5mg, 0.31mmol, 0.6eq.) and AIBN (4.6mg, 0.03mmol, 0.05eq.) in toluene and cyclohexane (1:1, 5 ml) was added

in the same way. After an additional period of 12 hours under reflux, the solvents were then evaporated under reduced pressure and the residue was purified by partition between acetonitrile and hexane (3x). The acetonitrile fraction then was concentrated and purified further by silica gel column chromatography (petroleum ether : ethyl acetate, 5:1, then acetonitrile followed with ethyl acetate) to give mixture of diastereomers of N-acetyl-2,5-dimethylpyrrolidine and the reduced product, 2-(acetylamino)-5-hexene (22mg, 31%) as a colourless oil.

ν_{max}(film)/cm^{-1} 2967, 2930 (C-H), 1631 (C=O); δ_H(400MHz, $CDCl_3$) *trans* isomer, 4.20 and 3.96 (2H, m, 2C***H***-CH_3), 2.06 (3H, s, C***H***$_3$CO), 2.23-2.03 and 1.52-1.46 (4H, m, 2C***H***$_2$), 1.13 (6H, d, *J*=6.5, 2C***H***$_3$); *cis* isomer, 4.09 and 3.88 (2H, m, 2C***H***-CH_3), 2.05 (3H, s, C***H***$_3$CO), 2.23-2.03 and 1.67-1.46 (4H, m, 2C***H***$_2$), 1.27 and 1.22 (6H, d, *J*=6.4, 2C***H***$_3$); δ_C(100MHz, $CDCl_3$)) *trans* isomer, 54.26 and 52.93 (***C***H-CH_3), 30.65 and 29.06 (2***C***H_2), 22.80 (***C***H_3CO), 21.23 and 19.02 (2***C***H_3); *cis* isomer, 54.80 and 50.54 (***C***H-CH_3), 31.87 and 31.00 (2***C***H_2), 22.22 (***C***H_3CO), 22.05 and 21.52 (2***C***H_3); *m/z* (CI) 142 (M^++1, 100%), 126 (20), 84 (45).

7.2.4.2. N-Pentanoyl-2,5-dimethylpyrrolidine [116b] and [117b]



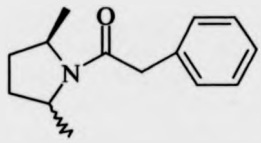
A solution of tributyltin hydride (131mg, 0.45mmol, 1.2 eq.) and AIBN (6.4mg, 0.04mmol, 0.1 eq.) in a deoxygenated mixture of cyclohexane (2.5 ml) and toluene

(2.5 ml) was added dropwise over 7 hours to a refluxing solution of pentanoic acid benzoyloxy-1-methylpent-4-enyl amide [107b] (125mg, 0.41mmol, 0.10M, 1eq.) in deoxygenated cyclohexane (5ml). After addition, the reaction was refluxed for a further 12 hours. A further amount of the solution of tributyltin hydride (73mg, 0.21mmol, 0.6eq.) and AIBN (5.5mg, 0.03mmol, 0.05eq.) in toluene and cyclohexane (1:1, 5 ml) was added in the same way. After an additional period of 12 hours under reflux, the solvents were then evaporated under reduced pressure and the residue was purified by soxhlet extraction (silica gel and cyclohexane refluxed for 24 hours, washed with dichloromethane and ethyl acetate). The resulted residue was then purified by partition between acetonitrile and hexane (3x). The acetonitrile fraction then was concentrated and purified further by silica gel column chromatography (petroleum ether : ethyl acetate, 5:1) to give mixture of diastereomers of N-pentanoyl - 2,5-dimethylpyrrolidine and the reduced product, 2-(pentanoylamino)-5-hexene (21mg, 27%) as a colourless oil. (Found MH^+ 184.1705, $C_{11}H_{22}NO$ requires 184.1701).

ν_{max}(film)/cm^{-1} 2960, 2928 (C-H), 1638 (C=O); δ_H(400MHz, $CDCl_3$) *trans* isomer, 4.21 and 4.00 (2H, m, 2C***H***-CH_3), 2.30 (2H, m, C***H₂***CO), 2.28-2.05 and 1.59-1.47 (4H, m, 2C***H₂***), 1.63 (2H, m, CH_2-C***H₂***-CH_2), 1.34 (2H, m, CH_3-C***H₂***-CH_2), 1.14 (6H, d, *J*=6.6, 2C***H₃***-CH), 0.90 (3H, t, *J*=7.3, C***H₃***-CH_2); *cis* isomer, 3.94 (2H, m, 2C***H***-CH_3), 2.30 (2H, m, C***H₂***CO), 2.28-2.05 and 1.67-1.59 (4H, m, 2C***H₂***), 1.63 (2H, m, CH_2-C***H₂***-CH_2), 1.34 (2H, m, CH_3-C***H₂***-CH_2), 1.28 and 1.21 (6H, d, *J*=6.4, 2C***H₃***-CH), 0.90 (3H, t, *J*=7.3, C***H₃***-CH_2); δ_C(100MHz, $CDCl_3$) *trans* isomer, 53.60 and 52.91 (***C***H-CH_3), 30.87 and 29.07 (2***C***H_2), 34.57, 27.88 and 22.60 (3***C***H_2), 21.80 and 19.24 (2***C***H_3-CH) 13.98 (***C***H_3-CH_2); *cis* isomer, 54.31 and 53.60 (***C***H-CH_3), 32.05 and

31.11 (2CH_2), 34.57, 27.88 and 22.60 (3CH_2), 22.67 and 21.88 (2CH_3.CH), 13.98 (CH_3-CH_2); *m/z* (CI) 184 (M^++1, 100%), 141 (45), 84 (71).

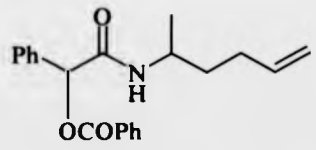
7.2.4.3. N-Phenylacetyl-2,5-dimethylpyrrolidine [116f] and [117f]



A solution of tributyltin hydride (104mg, 0.36mmol, 1.2 eq.) and AIBN (5mg, 0.03mmol, 0.1 eq.) in a deoxygenated mixture of cyclohexane (2.5 ml) and toluene (2.5 ml) was added dropwise over 7 hours to a refluxing solution of phenylacetic acid benzoyloxy-1-methylpent-4-enyl amide [107f] (100mg, 0.30mmol, 0.10M, 1eq.) in deoxygenated cyclohexane (3ml). After addition, the reaction was refluxed further for 12 hours. A further solution of tributyltin hydride (52mg, 0.18mmol, 0.6eq.) and AIBN (2.5mg, 0.015mmol, 0.05eq.) in toluene and cyclohexane (1:1, 5 ml) was added in the same way. After an additional period of 12 hours under reflux, the solvents were then evaporated under reduced pressure and the residue was purified by partition between acetonitrile and hexane (3x). The acetonitrile fraction then was concentrated and purified further by silica gel column chromatography (petroleum ether : ethyl acetate, 5:1, then ethyl acetate) to give mixture of diastereomers of N-phenylacetyl-2,5-dimethylpyrrolidine and the reduced product, 2-(phenylacetylamino)-5-hexene was collected (11mg, 16%) as a colourless oil. (Found MH+ 218.1541 , $C_{14}H_{20}NO$ requires 218.1545.)

ν_{max}(film)/cm^{-1} 3061, 3028 (=C-H), 2966, 2928 (C-H), 1636 (C=O); δ_H(400MHz, $CDCl_3$) *trans* isomer, 7.32-7.20 (5H, m, ***H***-Ar), 4.28 and 4.02 (2H, m, 2C***H***-CH_3), 3.66 (2H, s, CH_2Ph), 2.17-2.03 and 1.59-1.49 (4H, m, 2CH_2), 1.19 and 1.15 (6H, d, *J*=6.4, 2CH_3); *cis* isomer, 7.32-7.20 (5H, m, ***H***-Ar), 4.04 and 3.97 (2H, m, 2C***H***-CH_3), 3.52 (2H, s, CH_2Ph), 1.89-1.83 and 1.70-1.60 (4H, m, 2CH_2), 1.32 (6H, d, *J*=6.3, 2CH_3); δ_C(100MHz, $CDCl_3$) *trans* isomer, 169.53 (C=O) 135.96, 128.92, 128.87 and 126.62 (6***C*** of Ph), 53.79 and 53.25 (***C***H-CH_3), 41.45 (***C***H_2Ph), 30.88 and 29.07 (2***C***H_2), 21.98 and 18.98 (2***C***H_3); *cis* isomer, 169.33 (C=O) 135.56, 130.05, 128.91 and 128.14 (6***C*** of Ph), 54.42 and 54.01 (***C***H-CH_3), 41.67 (***C***H_2Ph), 32.00 and 31.09 (2***C***H_2), 22.30 and 21.87 (2***C***H_3); *m/z* (EI) 217 (M^+, 83%), 126 (55), 98 (72), 91 (100).

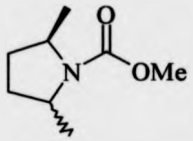
The rearrangement product, *N-(1-methylpent-4-enyl)-2-benzoyloxy-2-phenyl acetylamide* was furnished (30mg, 30%) as a white solid; mp 110-112 °C. (Found MH+ 338.1754, $C_{21}H_{24}NO_3$ requires 338.1756).



ν_{max}(film)/cm^{-1} 3278 (N-H), 2928, 2965 (C-H), 1721 (OC=O), 1657 (NC=O); δ_H(400MHz, $CDCl_3$) 8.11-7.30 (10H, m, 2C_6H_5), 6.29 (1H, s, C***H***-Ph), 6.00 (1H, br, N***H***), 5.80-5.65 (1H, m, C***H***=CH_2), 5.00-4.86 (2H, m, CH=CH_2), 4.05 (1H, m, C***H***-N), 2.09-1.95 (2H, m, CH_2-CH=), 1.60-1.47 (2H, m, -CH-CH_2), 1.14 (3H, dd, *J*=15.1, 6.7, CH_3-CH); δ_C(100MHz, $CDCl_3$) 167.69 (NC=O), 165.05 (OC=O), 137.80 (***C***H=CH_2), 135.69, 133.692, 129.86, 129.33, 128.84, 128.69, 128.30, 127.38 (8***C*** of 2Ph), 115.14

(CH=CH_2), 76.03 (*C*H-Ph), 45.13 (*C*H-N), 35.86, 30.14 (2CH_2), 20.71 (CH_3); *m/z* (CI) 338 (M^++1, 100%), 229 (85), 213 (82), 105 (22), 87 (48).

7.2.4.4. N-Methoxycarbonyl -2,5-dimethylpyrrolidine [116g] and [117g]

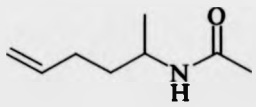


A solution of tributyltin hydride (192mg, 0.65mmol, 1.2 eq.) and AIBN (9mg, 0.05mmol, 0.1 eq.) in a deoxygenated mixture of cyclohexane (2.5 ml) and toluene (2.5 ml) was added dropwise over 7 hours to a refluxing solution of N-carbomethoxy benzoyloxy-1-methylpent-4-enyl amide [107g] (150mg, 0.54mmol, 0.10M, 1eq.) in deoxygenated cyclohexane (5ml). After addition, the reaction was refluxed further for 12 hours. After cooling, the solvents were then evaporated under reduced pressure and the residue was purified by soxhlet extraction (silica gel and hexane refluxed for 24 hours, then washed with dichloromethane and ethyl acetate). The residue was then purified by partition between acetonitrile and hexane (3x). The acetonitrile fraction then was concentrated and purified further by silica gel column chromatography (petroleum ether : ethyl acetate, 5:1, then ethyl acetate, followed with methanol). A mixture of diastereomers of N-methoxycabonyl-2,5-dimethylpyrrolidine was collected (11mg, 13% yield) as a colourless oil.

ν_{max}(film)/cm^{-1} 2957, 2920 (C-H), 1641 (C=O); δ_H(400MHz, $CDCl_3$) *trans* isomer, 4.00 and 3.91 (2H, m, 2C***H***-CH_3), 3.67 (3H, s, C***H***$_3$O), 2.11-2.08 and 1.54-1.47 (4H, m, 2C***H***$_2$), 1.16 and 1.09 (6H, d, *J*=6.4, 2C***H***$_3$); *cis* isomer, 3.93 and 3.89 (2H, m, 2C***H***-CH_3), 3.67 (3H, s, C***H***$_3$O), 2.02-1.92 and 1.60-1.56 (4H, m, 2C***H***$_2$), 1.19 (6H, d, *J*=6.2, 2C***H***$_3$); δ_C(100MHz, $CDCl_3$) *trans* isomer, δ: 53.52 and 53.06 (***C***H-CH_3), 51.85 (***C***H_3O), 30.34 and 29.45 (2***C***H_2), 20.46 and 19.50 (2***C***H_3); *cis* isomer, no ^{13}C NMR peaks of this isomer, due to the very small amount of the *cis* isomer in the cyclised products; ***m/z*** (EI) (M^+, 30%), 126 (50), 98 (100).

7.2.5 Experimental for the confirmation of cyclised products

7.2.5.1. N-1-Methyl pent-4-enyl acetamide [114a]

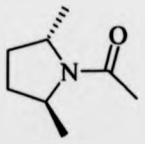


5-Hexen-2-one oxime [110] (2.5g, 22mmol) in diethyl ether (25ml) was added dropwise into a cooled solution of $LiAlH_4$ (2.6g, 68.5mmol) in ether (300 ml) at –78 °C under nitrogen. The reaction was allowed to warm to room temperature then equipped with a condenser and heated at reflux for 23 hours under nitrogen. After refluxing, the flask was cooled to –78 °C and the mixture was hydrolysed by dropwise addition of water (2.5 ml), NaOH (15%, 2.5 ml) and then water (7.5 ml). The reaction was again allowed to warm to room temperature and stirred overnight. The residue was treated with of a mixture of $MgSO_4$ and Na_2SO_4 (1: 1, 10g) and stirred for an

additional 11 hours. Then acetic anhydride (2.7g, 26.5mmol) was added and the solution was stirred for 18 hours. The resulting mixture was filtered and concentrated. This solution was washed with water, dried and evaporated. The N-1-methyl pent-4-enyl acetamide [114a] was collected in 74% yield (2.3g) as yellow oil which was used without further purification. The spectral data matched those published. [74]

ν_{max}(film)/cm^{-1} 3349 (C-H), 3250 (N-H), 1680 (C=O); δ_H(250MHz, $CDCl_3$) 6.44 (1H, br, N***H***), 5.57-5.60 (1H, m, C***H***=CH_2), 4.93-4.81 (2H, m, CH=C***H$_2$***), 3.96-3.78 (1H, m, NC***H***), 2.01-1.93 (2H, m, C***H$_2$***-CH=), 1.87 (3H, s, OCC***H$_3$***), 1.47-1.36 (2H, m, NCH-C***H$_2$***), 1.02 (3H, d, *J*=6.4, C***H$_3$***); δ_C(62.5MHz, $CDCl_3$) 169.51 (***C***=O), 137.87 (***C***H=CH_2), 114.58 (CH=***C***H_2), 44.70 (***C***H-N), 35.72, 30.22 (2***C***H_2), 23.16 (OC***C***H_3), 20.61 (***C***H_3); ***m/z*** (CI) 142 (M^++1, 100%), 99 (15), 114 (7).

7.2.5.2.N-Acetyl-*trans*-2,5,-dimethylpyrrolidine *(by amidomercuration)*

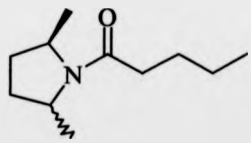


Mercuric acetate (2.6g, 8.2mmol) was added portionwise, to a stirred solution of 2-(acetylamino)-5-hexene (770mg, 5.4mmol) in THF (60ml). The mixture was purged with nitrogen, covered with aluminium foil and stirred for 18 hours. A solution of $NaBH_4$ (200mg, 5.3mmol) in aqueous NaOH (2.5M, 0.5ml) was added dropwise to the mixture. The reaction was stirred overnight, treated with saturated aqueous Na_2CO_3 (3ml) and stirred for an additional 4 hours. THF was removed under reduced pressure

and the residue was diluted with ether and extracted with saturated Na_2CO_3 (3x100ml). The aqueous layers were combined and extracted with dichloromethane. The combined organic fractions were dried over Mg_2SO_4 and concentrated. The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate, 5:1) to give N-acetyl-trans-2,5,-dimethylpyrrolidine (598mg, 78%) as a yellow oil. The spectral data matched those published.[74]

ν_{max}(film)/cm^{-1} 2968,2932 (C-H), 1630 (C=O); δ_H(400MHz, $CDCl_3$) 4.25-4.14 and 4.02-3.91 (2H, m, 2C***H***-CH_3), 2.06 (3H, s, C***H₃***CO), 2.27-2.02 and 1.60-1.50 (4H, m, 2C***H₂***), 1.16 (6H, d, *J*=6.4, 2C***H₃***); δ_C(100MHz, $CDCl_3$) 54.25 and 52.87 (***C***H-CH_3), 30.71 and 29.10 (2***C***H_2), 22.70 (***C***H_3CO), 21.32 and 19.10 (2***C***H_3); ***m/z*** (EI) 141 (M^+, 100%), 126 (50), 98 (35).

7.2.5.3. N-Pentanoyl-2,5-dimethylpyrrolidine *(by acylation)*

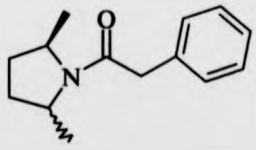


2,5-dimethylpyrrolidine (mixture of *cis* and *trans* isomer, 2:1) (50mg, 0.5 mmol) and triethylamine (0.2g, 2mmol) in benzene (1ml) was treated with pentanoyl chloride (0.31g, 2.5 mmol) at room temperature. The mixture was then allowed to stand for 30 minutes. The resulting solution was partitioned between aqueous 6M KOH and diethyl ether. The combined organic fractions were dried over $MgSO_4$ and concentrated. The

crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate, 5:1) to give he mixture of *cis* and *trans* (2:1) isomer of N-pentanoyl-2,5,-dimethylpyrrolidine (70mg, 76%) as light yellow oil. [73]

ν_{max}(film)/cm^{-1} 2960, 2927 (C-H), 1638 (C=O); δ_H(400MHz, $CDCl_3$) *trans* isomer, 4.23-4.18 and 4.03-3.97 (2H, m, 2C***H***-CH_3), 2.35-2.25 (2H, m, C***H***$_2$CO), 2.24-1.88 and 1.76-1.56 (4H, m, 2C***H***$_2$), 1.76-1.56 (2H, m, CH_2-C***H***$_2$-CH_2), 1.38-1.31 (2H, m, CH_3-C***H***$_2$-CH_2), 1.14 (6H, d, *J*=6.4, 2C***H***$_3$-CH), 0.90 (3H, t, *J*=7.3, C***H***$_3$-CH_2); *cis* isomer, 4.10-4.04 and 3.98-3.91 (2H, m, 2C***H***-CH_3), 2.35-2.25 (2H, m, C***H***$_2$CO), 2.24-1.88 and 1.76-1.56 (4H, m, 2C***H***$_2$), 1.76-1.56 (2H, m, CH_2-C***H***$_2$-CH_2), 1.38-1.31 (2H, m, CH_3-C***H***$_2$-CH_2), 1.27 and 1.22 (6H, d, *J*=6.2, 2C***H***$_3$-CH), 0.90 (3H, t, *J*=7.4, C***H***$_3$-CH_2); δ_C(100MHz, $CDCl_3$) *trans* isomer, δ: 53.70 and 53.01 (***C***H-CH_3), 30.84 and 29.06 (2***C***H_2), 34.55, 27.90 and 22.59 (3***C***H_2), 21.79 and 19.20 (2***C***H_3-CH) 13.96 (***C***H_3-CH_2); *cis* isomer, δ: 54.22 and 53.01 (***C***H-CH_3), 32.02 and 31.08 (2***C***H_2), 34.55, 27.90 and 22.59 (3***C***H_2), 22.68 and 22.44 (2***C***H_3.CH), 13.96 (***C***H_3-CH_2); *m/z* (EI) 183 (M^+, 100%), 141 (40) 126 (30), 98 (65), 84 (20).

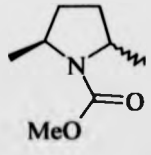
7.2.5.4. N-Phenylacetyl-2,5-dimethylpyrrolidine *(by acylation)*



Prepared using the above procedure (7.2.5.3) with phenylacetyl chloride (386mg, 2.5 mmol). The crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate, 5:1) to give the mixture of *cis* and *trans* (2:1) isomers of N-phenylacetyl-2,5,-dimethylpyrrolidine (184 mg, 34%) as a yellow oil.[73]

ν_{max}(film)/cm^{-1} 3060, 3028 (=C-H), 2966, 2928 (C-H), 1632 (C=O); δ_H(400MHz, $CDCl_3$) *trans* isomer, 7.25-7.15 (5H, m, ***H***-Ar), 4.19 and 4.06 (2H, m, 2C***H***-CH_3), 3.65 (2H, s, CH_2Ph), 2.08-1.96 and 1.56-1.47 (4H, m, 2CH_2), 1.15 and 1.10 (6H, d, *J*=6.4, 2CH_3); *cis* isomer, 7.25-7.15 (5H, m, ***H***-Ar), 4.05 and 3.96 (2H, m, 2C***H***-CH_3), 3.60 (2H, s, CH_2Ph), 1.84-1.77 and 1.62-1.57 (4H, m, 2CH_2), 1.26 and 1.14 (6H, d, *J*=6.3, 2CH_3), δ_C(100MHz, $CDCl_3$) *trans* isomer, δ: 169.50 (C=O) 135.86, 128.80, 128.75 and 126.53 (6***C*** of Ph), 53.65 and 53.15 (***C***H-CH_3), 41.32 (***C***H_2Ph), 30.75 and 28.97 (2***C***H_2), 21.87 and 18.85 (2***C***H_3); *cis* isomer, δ: 169.37 (C=O) 135.45, 129.95, 128.83 and 128.03 (6***C*** of Ph), 54.32 and 53.95 (***C***H-CH_3), 41.59 (***C***H_2Ph), 31.99 and 30.95 (2***C***H_2), 22.20 and 21.75 (2***C***H_3); *m/z* (EI) 217 (M^+, 80%), 126 (45), 98 (100), 91 (80).

7.2.5.5.N-Methoxycarbonyl-2,5,-dimethylpyrrolidine *(by acylation)*



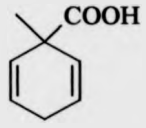
Prepared using the 7.2.5.3 procedure with methylchloroformate (400mg, 4mmol) and 2,5-dimethylpyrrolidine (mixture of *cis* and *trans* isomer, 2:1) (100mg, 1mmol). The

crude product was purified by silica gel chromatography (petroleum ether: ethyl acetate, 5:1) to give the mixture of *cis* and *trans* isomer (2:1) of N-methoxycarbonyl-2,5,-dimethylpyrrolidine (56mg, 36%) as a colourless oil. [73]

ν_{max}(film)/cm^{-1} 2950, 2918 (C-H), 1645 (C=O); δ_H(400MHz, $CDCl_3$) *trans* isomer, 4.05-3.72 (2H, br, m, 2C***H***-CH_3), 3.65 (3H, s, C***H₃***O), 2.11-2.03 and 1.50-1.45 (4H, m, 2C***H₂***), 1.13 and 1.09 (6H, d, *J*=6.4, 2C***H₃***); *cis* isomer, 3.91 and 3.72 (2H, m, 2C***H***-CH_3), 3.65 (3H, s, C***H₃***O), 2.00-1.87 and 1.65-1.52 (4H, m, 2C***H₂***), 1.19 (6H, d, *J*=6.1, 2C***H₃***); δ_C(100MHz, $CDCl_3$) *trans* isomer, δ: 54.37 and 52.92 (***C***H-CH_3), 51.74 (***C***H_3O), 30.17 and 29.30 (2***C***H_2), 20.29 and 19.33 (2***C***H_3); *cis* isomer, δ: 54.19 (br, ***C***H-CH_3), 51.81 (br, ***C***H_3O), 31.59 (br, 2***C***H_2), 21.81 (br, 2***C***H_3); *m/z* (EI) 157 (M^+, 80%), 126 (100), 98 (70).

7.3. Experimental for chapter 3

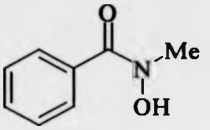
7.3.1. 1-methyl-2,5-cyclohexadiene-1-carboxylic acid [145]



Small pieces of lithium (1.12g, 0.16mol) were added to a stirred solution of benzoic aid (6.5g, 53mmol) in liquid ammonia (250 ml) at –78°C under nitrogen. Iodomethane was then added dropwise and the mixture was allowed to stir at this temperature for 15 minutes. The ammonia was then allowed to evaporate by warming to room teemperarure. The residue was treated with water, acidified with 20% aqueous hydrochloric acid and extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate and concentrated to afford 1-methyl-2,5-cyclohexadiene-1-carboxylic acid (6.14g, 84%) as yellow oil. The carboxylic acid was then used without further purification. [82]

ν_{max}(film)/cm^{-1} 3033 (O-H), 1701 (C=O); δ_H(250MHz, $CDCl_3$) 5.88-5.74 (4H, m, 2x*CH*=*CH*), 2.61-2.69 (2H, m, CH_2), 1.42 (3H, s, CH_3); δ_C(62.5MHz, $CDCl_3$) 181.86 (*C*=O), 127.94, 124.84 (*C*H=*C*H), 43.56 (*C*-CO), 27.11 (CH_2), 25.75 (CH_3); *m/z* (CI) 139 (M^++1, 100%), 105 (92), 95 (49).

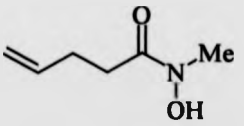
7.3.2. N-Hydroxy-N-methyl benzoamide [144a]



Benzoyl chloride (1.0g, 9.6mmol) in diethyl ether (10ml) was added dropwise to a stirred suspension of sodium carbonate (2.0g, 19mmol) and methyl hydroxylamine hydrochloride (7.8g, 9.4mmol) in diethyl ether (40ml) over 15 minutes at 0°C. The mixture was then allowed to warm to room temperature and stir for a further 18 hours. Water (20ml) was added and the organic layer was quick extracted with diethyl ether, washed with diluted HCl and concentrated. The N-hydroxy-N-methyl benzoamide [144a] was collected (710mg, 50%) which was used with out further purification. [106]

ν_{max}(film)/cm^{-1} 3188 (O-H), 2924 (C-H), 1601 (C=O); δ_H(250MHz, $CDCl_3$) 7.61-7.31 (5H, m, 4x ***H***-Ar and OH), 3.36 (3H, s, C***H₃***); δ_C(62.5MHz, $CDCl_3$) 171.60 (***C***=O), 134.56, 133.34, 130.25 and 128.60 (6***C*** of Ar), 38.96 (***C***H_3); *m/z* (CI) 152 (M^++1, 13%), 136 (100), 122 (75), 105 (47), 44 (77).

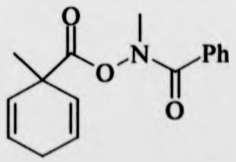
7.3.3. N-Hydroxy-N-methyl pent-4-enamide [144b]



Pentanoyl chloride (1.1g, 9.4mmol) in diethyl ether (10ml) was added dropwise to the stirred suspension of sodium carbonate (2.0g, 19mmol) and methyl hydroxylamine hydrochloride (7.8g, 9.4mmol) in diethyl ether (40ml) over 15 minutes at 0°C. The mixture was then allowed to warm to room temperature and stir further for 18 hours. Water (20ml) was added and the organic layer was quick extracted with diethyl ether, washed with diluted HCl and concentrated. The N-hydroxy-N-methyl pent-4-enamide [144b] was collected (734mg, 61%) which was used with out further purification.

ν_{max}(film)/cm^{-1} 3178 (O-H), 2926 (C-H), 1618 (C=O); δ_H(250MHz, $CDCl_3$) 9.44 (1H, br, O*H*), 5.81-5.68 (1H, m, C*H*=), 5.09-4.90 (2H, m, CH_2=), 3.17 (3H, s, CH_3), 2.56-2.48, 2.44-2.22 (4H, m, 2xCH_2); δ_C(62.5MHz, $CDCl_3$) 173.94 (*C*=O), 137.05 (*C*H=), 115.04 (*C*H_2=), 35.97, 31.27 (2x*C*H_2), 28.55 (*C*H_3); *m/z* (CI) 130 (M^++1, 25%), 114 (100), 102 (63), 83 (100).

7.3.4. N-Methyl-N-(1-methyl-2,5-cyclohexadiene-1-carboxyloxy) benzoamide |142a|



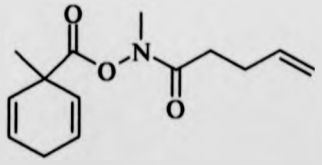
1-Methyl-2,5-cyclohexadiene-1-carboxylic acid (1.0g, 7.2mmol) was refluxed with excess oxalyl chloride (3g, 24mmole) for one hour. Excess oxalyl chloride was removed under reduced pressure and the residue distilled under reduced pressure to

give 1-Methyl-2,5-cyclohexadiene-1-carboxyl chloride (1.1g, 93%) as a yellow oil which was used immediately.

1-Methyl-2,5-cyclohexadiene-1-carboxyl chloride (254mg, 1.5mmol) in dichloromethane (10ml) was added to a solution of benzoyl methyl hydroxyamide (222mg, 1.5mmol) and pyridine (116mg, 1.5mmol) in dichloromethane (40ml) over 15 minutes at room temperature. The reaction was allowed to stir for 20 hours. The mixture was then concentrated and purified by silica gel column chromatography (petroleum ether:ethyl acetate, 5:1) to afford benzoic acid N-methyl-N-(1-methyl-2,5-cyclohexadiene-1-carboxyloxy) benzoamide [142a] as colourless oil (230mg, 58%). (Found MH^+ 127.1205, $C_{16}H_{17}NO_3$ requires 217.1208).

ν_{max}(film)/cm^{-1} 2925 (C-H), 1765, 1695 (C=O); δ_H(250MHz, $CDCl_3$) 7.49-7.30 (m, 5H, ***H***-Ar), 5.73-5.68, 5.45-5.40 (m, 4H, C***H***=C***H***), 3.32 (s, 3H, C***H₃***-N), 2.53 (m, 2H, C***H₂***), 1.06 (s, 3H, C***H₃***); δ_C(62.5MHz, $CDCl_3$) 172.28, 171.42 (***C***=O), 133.25, 130.63, 129.74, 127.30, 126.55 and 125.53 (4***C*** of Ar and ***C***H=***C***H), 42.90 (***C***H_3-N), 26.41 (***C***H_2), 25.55 (***C***H_3); ***m/z*** (CI) 272 (M^++1, 31%), 256 (46), 136 (100), 105 (53).

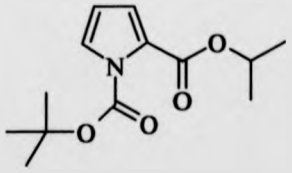
7.3.5. N-Methyl-N-(1-methyl-2,5-cyclohexadiene-1-carboxyloxy) pent-4-enamide [142a]



1-Methyl-2,5-cyclohexadiene-1-carboxyl chloride (308mg, 2.0mmol) in dichloromethane (10ml) was added to a solution of methyl pentanoyl hydroxylamide (231mg, 1.8mmol) and pyridine (142mg, 1.8mmol) in dichloromethane (40ml) over 15 minutes at room temperature. The reaction was allowed to stir for 20 hours. The mixture was then concentrated and purified by silica gel column chromatography (petroleum ether : ethyl acetate, 5:1) to afford N-methyl-N-(1-methyl-2,5-cyclohexadiene-1-carboxyloxy) pent-4-enamide [142a] as colourless oil (213mg, 48%). (Found MH+ 249.1370, $C_{14}H_{19}NO_3$ requires 249.1365).

ν_{max}(film)/cm^{-1} 2929 (C-H), 1703, 1618 (C=O); δ_H(250MHz, $CDCl_3$) 5.74-5.65 (5H, m, 2x*CH*=*CH* and *CH*=), 5.00-4.89 (2H, m, CH_2=), 3.19 (3H, s, CH_3-N), 2.67-2.62 (2H, m, =CH-CH_2-CH=), 2.36-2.19 (4H, m, 2x CH_2), 1.38 (3H, s, CH_3); δ_C(62.5MHz, $CDCl_3$) 179.12, 172.14 (*C*=O), 136.74 (*C*H=CH_2), 128.30, 126.59, 125.87 and 124.37 (4C of *C*H=*C*H), 115.29 (CH=*C*H_2), 43.14 (*C*H_3-N), 31.10, 28.46 and 26.53 (3x *C*H_2), 25.62 (*C*H_3); *m/z* (CI) 250 (M^++1, 62%), 130 (71), 114 (100), 91 (45).

7.3.6. Isopropyl N-(*tert*–butoxycarbonyl) pyrrole-2-carboxylate [158]



Trichloroacetyl pyrrole (5g, 23.7 mmol) was suspended in water (5 ml) and KOH (1.33g, 23.7 mmol) was added. The reaction was heated at 80°C for 18 hours and excess water removed by azeotropic distillation with toluene. The potassium salt was dried under vacuum for 12 hours and then suspended in dichloromethane (15 ml). Oxalyl chloride (3 ml, 35.5 mmol) was added dropwise to the mixture at 0°C and after 30 minutes the reaction was refluxed for 3 hours. Excess oxalyl chloride was removed in vacuo and the acid chloride was then dissolved in isopropyl alcohol (10ml) and heated at reflux for 12 hours. Excess isopropyl alcohol was evaporated to afford the pyrrolisopropyl ester [157] (20.26g, 85%) as a dark viscous oil.

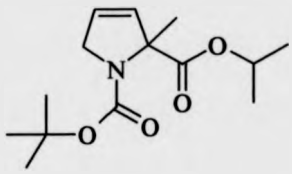
δ_H(300MHz, $CDCl_3$) 9.54 (1H, br, N***H***), 6.94-6.84 (2H, m, ***H***-Ar), 6.28-6.22 (1H, m, ***H***-Ar), 5.24-5.14 (1H, m, C***H***-CH_3), 1.32 (6H, d, *J*= 6.15, 2C***H***$_3$).

A solution of the pyrrole isopropyl ester (2.5 g, 16.3 mmol) in THF (5ml) was added to NaH (782mg, 32.6mmol) in THF (10ml) at room temperature. After 30 minutes, di-*tert*-butyl dicarbonate (9 ml, 39.1 mmol) was added slowly and the reaction heated at 45°C for 12 hours. The reaction mixture was then diluted with water (10ml), extracted with dichloromethane (3x30ml). The combined organic fractions were dried with $MgSO_4$ and concentrated in *vacuo*. The resulted residue was purified by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) to afford the N-Boc pyrrole isopropyl ester (3.11g, 75%) as a pale yellow oil. [83b]

ν_{max}(film)/cm^{-1} 2980, 2934 (C-H), 1752, 1718 (C=O); δ_H(300MHz, $CDCl_3$) 7.20 (1H, dd, J= 3.2, 1.7, ***H***-Ar), 6.71 (1H, dd, J= 3.6, 1.7, ***H***-Ar), 6.06 (1H, t, J= 3.4 Hz, ***H***-Ar), 5.06 (1H, m, C***H***CH_3), 1.50 and 1.44 (9H, s, $3CH_3C$), 1.24 (6H, d, J= 6.4, 2C***H***$_3$CH);

δ_C(75MHz, $CDCl_3$) 160.19 (*C*=O), 146.65, 129.35, 120.30 and 109.88 (4*C* of Ar), 84.147 (*C*CH_3), 68.08 (C*H*CH_3), 27.52 and 21.75 (5*C*H_3).

7.3.7. N-(tert-Butoxycarbonyl)-2-(isopropoxycarbonyl)-2-methyl-2,5-dihydropyrrole



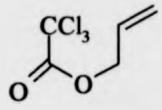
A solution of the N-Boc pyrrole ester [158] (0.5g, 2.0 mmol) in THF (10ml) was added rapidly to a mixture of ammonia (150ml), THF (40 ml) and sodium (136 mg, 6.0 ml) at –78°C. After 5 minutes, methyl iodide (1ml) was added and after a futher 2 h, NH_4Cl (excess) was added. The mixture was slowly warmed to room temperature, while the ammonia was removed with a stream of nitrogen. Brine was added and the product extracted with EtOAc (3x 50ml). The combined organic fractions was dried and concentrated under reduced pressure. Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the dihydropyrrole (124mg, 23%) as a colourless oil. [83b]

ν_{max}(film)/cm^{-1} 2977, 2933 (C=H), 1723, 1700 (C=O); δ_H(300MHz, $CDCl_3$) 5.40 (1H, br, d, =C*H*C), 5.47-5.21 (1H, m, =C*H*-CH_2), 5.00-4.92 (1H, m, C*H*CH_3), 3.80 (2H, br, CH_2N), 1.40 (9H, s, 3CH_3), 1.30 (3H, s, CH_3), 1.19 (6H, d, J= 6.4, 2CH_3); δ_C(75MHz,

$CDCl_3$) 176.14 and 155.36 (2*C*=O), 136.18 and 128.13 (2*C*H=), 79.22 (*C*CH_3), 67.76 (*C*H_2), 42.83 (*C*$(CH_3)_3$), 33.34 (*C*H$(CH_3)_2$), 28.18, 26.72 and 21.41 (5*C*H_3).

7.4. Experimental of chapter 4

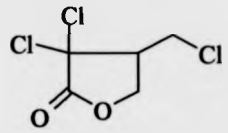
7.4.1. Allyl trichloroacetate [30]



Trichloroacetyl chloride (15.7g, 86mmol) in diethyl ether (20ml) was added dropwise to a solution of allyl alcohol (5.0g, 86mmol) and pyridine (7g, 86mmol) in diethyl ether (30ml) at –78 °C. The mixture was allowed to warm to room temperature and stir for 2 hours. The solution was concentrated and dichloromethane was added. The resulting mixture was washed with diluted HCl and saturated sodium hydrogen carbonate. The organic layer was dried over magnesium sulfate and concentrated. The resulting oil was purified by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) to afford the allyl trichloroacetate [30] (14.00g, 80%) as colourless oil.

ν_{max}(film)/cm^{-1} 1770 (C=O); δ_H(400MHz, $CDCl_3$) 6.04-5.88 (1H, m, C*H*=CH2), 5.50-5.37 (2H, m, CH=CH_2), 4.82 (2H, d, J=5.8, CH_2); δ_C(100MHz, $CDCl_3$) 161.42 (C=O), 129.71 (*C*H=CH_2), 129.11 (CH=*C*H_2), 89.55 (*C*Cl_3), 69.20 (*C*H_2); *m/z* (Cl) 220(M^++17,64%), 81 (100).

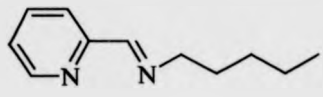
7.4.2. General procedure for the cyclisation of Allyl trichloroacetate [31]



CuCl was stirred under nitrogen for 30 min. Solvent was then added. The solution of allyl trichloroacetate in solvent was added dropwise. The solution of ligand in solvent was then added immediately. The mixture was heated at reflux for 4 hours. The reaction was allowed to cool to room temperature and filtered through a short silica gel column, eluting with dichloromethane to remove metallic species. The resulting oil was purified further by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) to afford the lactone [31] as a white solid; mp 71-72 °C. (Found C, 29.89; H, 2.48; Calc. for $C_5H_5O_2Cl_3$: C, 29.52; H, 2.48). [27]

ν_{max}(film)/cm^{-1} 1725 (C=O); δ_H(400MHz, $CDCl_3$) 4.65 (1H, dd, J=9.5, 7.0, C***H***$_2$-O), 4.22 (1H, t, J=8.4, C***H***$_2$-O), 3.97 (1H, dd, J=11.2, 4.5, C***H***$_2$-Cl), 3.72 (1H, dd, J=11.5, 9.8, C***H***$_2$-Cl), 3.36-3.29 (1H, m, C***H***); δ_C(100MHz, $CDCl_3$) 166.98 (***C***=O), 100.19 (***C***Cl_2), 68.57 (***C***H_2-O), 53.22 (***C***H), 39.54 (***C***H_2Cl).

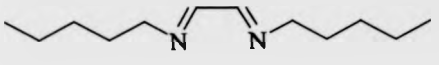
7.4.3. N-Pentyl-2-pyridylmethanimine [164]



n-Pentylamine (8.14g, 93.4mmol) was added to a solution of 2-pyridine carbaldehyde (10g, 93.4mmol) in diethyl ether (20ml). The solution was stirred at room temperature for 10 minutes and magnesium sulfate (20g) was added. This suspension was left for 2 hours to remove all the water produced from the reaction. The diethyl ether was removed in *vacuo* to give a yellow liquid which was then purified by vacuum distillation to give N-pentyl-2-pyridylmethanimine (10.12g, 62%) as a light yellow oil. [87]

ν_{max}(film)/cm^{-1} 1649 (C=N), 1587, 1567, 1467 (C=C); δ_H(250MHz, $CDCl_3$) 8.60 (1H, d, J= 4.5, ***H***-Ar), 8.26 (1H, s, ***H***C=N), 7.95 (1H, d, J=7.9, ***H***-Ar), 7.70 (1H, t, J= 7.5, ***H***-Ar), 7.27 (1H, t, J=5.5, ***H***-Ar), 3.54 (2H, t, J=6.9, C***H***$_2$-N), 1.63-1.59 (2H, m, C***H***$_2$-CH_2N), 1.26-1.22 (4H, m, 2 x C***H***$_2$), 0.78 (3H, t, J= 6.8, C***H***$_3$); δ_C(100MHz, $CDCl_3$) 161.89, 154.93, 149.62, 136.74, 124.83 and 121.43 (5***C*** of Ar and ***C***H=N), 61.82 (***C***H_2-N), 30.66, 29.78 and 22.75 (3 x ***C***H_2), 14.31 (***C***H_3); ***m/z*** (EI) 176(M^+,30%) 119 (100), 92 (50), 71 (27).

7.4.4. 1,4-dipentyl-1,4-diazobuta-1,3-diene [165]



Pentylamine (12g, 0.13mol) was added dropwise to a solution of 40% aqueous glyoxal (10g, 0.07mol). After 10 minutes two layers formed. The aqueous layer was extracted with diethyl ether (3x 100ml) and the combined organic fractions were added magnesium sulfate (20g). This suspension was left for 2 hours then filtered and solvent was removed in *vacuo* to leave a yellow liquid. Vacuum distillation afforded 1,4-dipentyl-1,4-diazobuta-1,3-diene (12.20g, 48%) as a pule yellow liquid. [85]

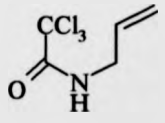
ν_{max}(film)/cm^{-1} 1670 (C=N); δ_H(250MHz, $CDCl_3$) 7.88 (2H, s, 2xC***H***N), 2.68-2.48 (4H, m, 2xC***H$_2$***-N), 1.43-1.18 (12H, m, 6xC***H$_2$***), 0.89 (6H, t, J=7.0, 2xC***H$_3$***); δ_C(62.5MHz, $CDCl_3$) 1.66.80 (2 x ***C***HN), 60.62 (2 x ***C***H$_2$-N), 32.99, 31.22 and 20.75 (6 x ***C***H$_2$), 14.32 (2 x ***C***H$_3$); *m/z* (EI) 196 (M^+, 77%), 139 (45), 82 (100).

7.5. Experimental for chapter 5

7.5.1.General procedure for the preparation of N-allyl trichloroacetamides

Trichloroacetyl chloride (1 eq.) in diethyl ether was added dropwise to a solution of allylamine (1 eq.) in THF at room temperature. The mixture was allowed to warm to room temperature and stir for 2 hours. The solution was concentrated in *vacuo* and dichloromethane was added. The resulting solution was washed with diluted HCl and saturated sodium hydrogen carbonate. The organic layer was dried over magnesium sulfate and concentrated.

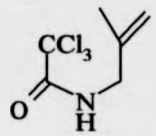
7.5.1.1. N-Allyl trichloroacetamide [174]



Allylamine (3.0g, 52mmol) was reacted with trichloroacetyl chloride (9.5g, 52mmol) in the presence of pyridine (4.0g, 52mmol) in THF (50ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave the N-allyl trichloroacetamide as a white solid (7.10g, 67%g); mp 45-47 °C. (Found: C, 29.74; H, 2.95; N, 6.71. Calc. for $C_5H_6NOCl_3$: C, 29.70; H, 3.00; N, 6.90%).

ν_{max}(film)/cm^{-1} 3332 (N-H), 2920, 2853 (C-H), 1644 (C=O); δ_H(250MHz, $CDCl_3$) 6.88 (1H, br, N***H***), 5.93-5.78 (1H, m, C***H***=CH_2), 5.29-5.19 (2H, m, CH=C***H$_2$***), 3.97 (2H, t, J=5.5, C***H$_2$***); δ_C(62.5MHz, $CDCl_3$) 132.03 (***C***H=CH_2), 117.54 (CH=***C***H_2), 92.37 (***C***Cl_3), 43.39 (***C***H_2); ***m/z*** (CI) 202 (M^++1, 49%), 168 (100), 138 (42).

7.5.1.2. N-2-Methyl-prop-2-enyl trichloroacetamide [176a]



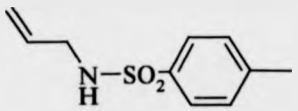
2-Methylallylamine hydrochloride (5.0g, 46mmol) was reacted with trichloroacetyl chloride (8.5g, 47mmol) with the present of triethylamine (9.5g, 94mmol) in THF (50ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) gave the N-2-methyl-prop-2-enyl trichloroacetamide [176a] (8.75g, 87%) as yellow oil.

ν_{max}(film)/cm^{-1} 3357 (N-H), 1649 (C=O); δ_H(250MHz, $CDCl_3$) 7.60 (1H, br, N***H***), 4.86 (2H, s, C***H$_2$***=), 3.87 (2H, d, J=5.8, C***H$_2$***), 1.72 (3H, s, C***H$_3$***); δ_C(62.5MHz, $CDCl_3$) 162.01 (C=O), 140.00 (=***C***-), 111.80 (=***C***H_2), 92.50 (***C***Cl_3), 43.39 (***C***H_2), 20.81 (***C***H_3); ***m/z*** (EI) 216 (M^+, 90%), 182 (92), 55 (100).

7.5.2. General procedure for the preparation of N-allyl-N-tosylamides

Allylamine (1eq.) was added dropwise to a stirred solution of *p*-toluenesulphonyl chloride (1 eq.) and triethylamine (2eq.) in THF at room temperature. The mixture was allowed to stir at this temperature for 4 hours. The resulting solution was then concentrated, dissolved in water, extracted with diethyl ether, dried over magnesium sulfate and concentrated. [32]

7.5.2.1. N-Allyl-N-tosylamide [171]

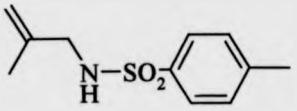


Allylamine (3.05g, 53mmol) was reacted with *p*-toluenesulphonyl chloride (10g, 53mmol) and triethylamine (5.5g, 54 mmol) in THF (50 ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-allyl-tosylamide (8.90g, 80%) as white solid; 101-103 °C. (Found: C, 56.60; H, 6.13; N, 6.40. Calc. for $C_{10}H_{13}NO_2S$: C, 56.80; H, 6.20; N, 6.60%).

ν_{max}(film)/cm^{-1} 3424 (N-H), 2951, 2921, 2851, (C-H), 1644 (C=C); δ_H(250MHz, $CDCl_3$) 8.14 and 7.68 (4H, d, J= 8.5, ***H***Ar), 6.17-6.01 (1H, m, C***H***=CH_2), 5.58-5.42 (2H, m, CH=C***H***$_2$), 5.35 (1H, br, N***H***) 3.94 (2H, t, J=5.8, C***H***$_2$), 2.80 (3H, s, C***H***$_3$); δ_C(62.5MHz, $CDCl_3$) 143.28 (1***C*** of Ar), 136.76 (***C***H=CH_2), 132.81, 129.53 and

126.96 (5*C* of Ar), 117.41 (CH=*C*H_2), 45.54 (*C*H_2), 21.32 (*C*H_3); *m/z* (EI) 211(M^+, 13%), 155 (520, 91 (100), 56 (86).

7.5.2.2. N-2-Methyl prop-2-enyl-N-tosylamide



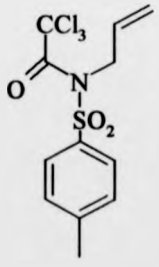
2-Methylallyamine hydrochloride (5.8g, 54mmol) was reacted with *p*-toluenesulphonyl chloride (10.2g, 54mmol) and triethylamine (20g, 198mmol) in THF (50 ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-2-methyl prop-2-enyl-N-tosylamide (10.90g, 90%) as white solid; mp 102-104 °C. (Found: C, 58.64; H, 6.69; N, 5.99. Calc. for $C_{11}H_{15}NO_2S$: C, 58.60; H, 6.70; N, 6.20%).

ν_{max}(film)/cm^{-1} 3460 (N-H), 2919, 2853 (C-H); δ_H(250MHz, $CDCl_3$) 7.74 and 7.29 (d, 4H, *J*= 8.2, *H*Ar), 4.83 and 4.81 (2H, s, =C*H*$_2$), 4.67 (1H, br, N*H*) 3.46 (2H, d, *J*=4.4, 2H, C*H*$_2$), 2.41 (3H, s, C*H*$_3$-Ar), 1.66 (3H, s, C*H*$_3$); δ_C(62.5MHz, $CDCl_3$) 143.80 (1*C* of Ar), 140.88(-*C*=), 137.31, 130.08, and 127.51 (5*C* of Ar), 113.10 (=*C*H_2), 49.38 (*C*H_2), 21.91 (*C*H_3-Ar), 20.50 (*C*H_3); *m/z* (EI) 225 (M^+, 24%), 155 (64), 91 (97), 70 (100).

7.5.3.General procedure for the preparation of N-allyl-N-tosyl-N-tri-,or dihaloamides

n-BuLi (2.5M in hexane) was added to a solution of N-allyltosylamide in diethyl ether at –78 °C and the solution was stirred at this temperature for 30 min. Tri-, or dihaloacetyl chloride was added and the mixture was then stirred for 2 hours at room temperature. Excess base was quenched with saturated aqueous NH_4Cl and the mixture was quickly extracted with diethyl ether (3x100ml). The combined extracts were washed with 1N NaOH and 1N NaCl, dried and concentrated.[36]

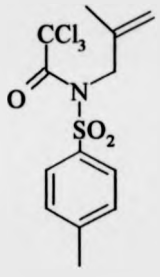
7.5.3.1. N-Allyl-N-tosyl trichloroacetamide [172]



N-Allyl-tosylamide (4.32g, 20mmol) in ether was reacted with a hexane solution 2.5M of n-BuLi (8ml, 20mmol) then with trichloroacetyl chloride (3.75g, 21mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-allyl-N-tosyl trichloroacetamide (6.34g, 89%) as white solid; mp 74-75 °C. (Found: C, 40.45; H, 3.35; N, 3.92. Calc. for $C_{12}H_{12}NO_3SCl_3$: C, 40.40; H, 3.40; N, 3.90%).

ν_{max}(film)/cm^{-1} 2925. (C-H), 1752 (C=O); δ_H(250MHz, $CDCl_3$) 7.91 (2H, d, *J*= 8.5, *H*Ar), 7.35 (2H, d, *J*= 8.5, *H*Ar), 6.02-5.87 (1H, m, C*H*=CH_2), 5.48-5.34 (2H, m, CH=CH_2), 4.91 (2H, d, *J*=5.5, CH_2), 2.44 (3H, s, CH_3); δ_C(62.5MHz, $CDCl_3$) 158.81 (*C*=O), 145.53 (1*C* of Ar), 134.60 (*C*H=CH_2), 132.18, 129.36, and 129.32 (5*C* of Ar), 119.33 (CH=*C*H_2), 91.97 (*C*Cl_3), 50.97 (*C*H_2), 21.60 (*C*H_3); *m/z* (CI) 372 (M^++17, 100%), 336 (70), 300 (31).

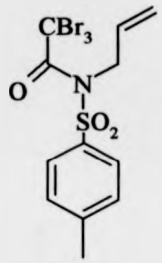
7.5.3.2. N-2-Methyl prop-2-enyl-N-tosyl trichloroacetamide [176b]



N-Allyl-tosylamide (1.80g, 8mmol) in ether was reacted with a hexane solution 2.5M of n-BuLi (3.20ml, 8mmol) then with trichloroacetyl chloride (1.5g, 8mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-2-methyl prop-2-enyl-N-tosyl trichloroacetamide [176b] (2.40g, 81%) as white solid; 81-83 °C. (Found: C, 46.16; H, 4.67; N, 4.24. Calc. for $C_{13}H_{14}NO_3SCl_3$: C, 46.12; H, 4.20; N, 4.10%).

ν_{max}(film)/cm^{-1} 2924 (C-H), 1716 (C=O); δ_H(400MHz, $CDCl_3$) 7.91 (2H, d, *J*= 8.2, ***H***Ar), 7.32 (2H, d, *J*= 8.2, ***H***Ar), 4.84 and 4.67 (2H, s, =C***H***$_2$), 4.75 (2H, s, C***H***$_2$), 2.44 (3H, s, C***H***$_3$-Ar), 1.77 (3H, s, C***H***$_3$); δ_C(100MHz, $CDCl_3$) 159.25 (***C***=O), 145.64 (1***C*** of Ar), 139.52 (-***C***=), 134.47, 129.52 and 129.35 (5***C*** of Ar), 112.41 (=***C***H$_2$), 89.51 (***C***Cl$_3$), 53.69 (***C***H$_2$), 21.72 (***C***H$_3$-Ar), 20.29 (***C***H$_3$); ***m/z*** (EI) 369 (M^+, 100%), 155 (59), 91 (90).

7.5.3.3. N-Allyl-N-tosyl tribromoacetamide [191]

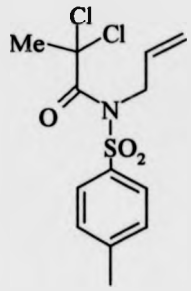


N-Allyl-tosylamide (2.0g, 9.5mmol) in ether was reacted with a hexane solution 2.5M of n-BuLi (3.80ml, 9.5mmol) then with tribromoacetyl chloride (3.0g, 9.5mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-allyl-N-tosyl tribromoacetamide (3.70g, 79%g) as white solid; mp 59-60 °C. (Found: C, 29.43; H, 2.30; N, 2.89. Calc. for $C_{12}H_{13}NO_3SBr_3$: C, 29.35; H, 2.67; N, 2.85%). (Found M+ 487.4180, $C_{12}H_{13}NO_3SBr_3$ requires 487.4185).

ν_{max}(film)/cm^{-1} 1703 (C=O); δ_H(250MHz, $CDCl_3$) 7.90 (2H, d, *J*= 8.2, ***H***Ar), 7.30 (2H, d, *J*= 8.2, ***H***Ar), 6.05-5.91 (1H, m, C***H***=CH$_2$), 5.49-5.34 (2H, m, CH=C***H***$_2$), 4.96 (2H, d, *J*=5.4, C***H***$_2$), 2.42 (3H, s, C***H***$_3$); δ_C(62.5MHz, $CDCl_3$) 164.25 (***C***=O), 135.18

(1*C* of Ar), 132.60 (*C*H=CH_2), 133.40, 129.85, and 128.69 (5*C* of Ar), 119.90 (CH=*C*H_2), 90.00 (*C*Cl_3), 49.74 (*C*H_2), 22.16 (*C*H_3); *m/z* (EI) 490 (M^+, 65%), 410 (100).

7.5.3.4. N-Allyl-N-tosyl-dichloromethylacetamide [49]



2,2-Dichloropropionic acid (5g, 35mmol) was refluxed with excess oxalyl chloride (6g, 47mmole) for 1.5 hours. Excess oxalyl chloride was removed under pressure and the residue distilled under reduced pressure. 2,2-Dichloropropionyl chloride was collected in 94% yield (5.3g) as a colourless liquid which was used immediately.

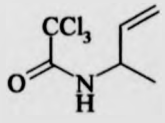
N-Allyl-tosylamide (4.0g, 19mmol) in ether was reacted with a hexane solution 1.6M of n-BuLi (12.5ml, 20mmol) then with 2,2 dichloropropionyl chloride (3.04g, 19mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-allyl-N-tosyl-dichloromethylacetamide [49] (5.46g, 86%) as white solid; mp 79-80 °C. (Found: C, 46.42; H, 4.49; N, 3.98. Calc. for $C_{13}H_{15}NO_3SCl_2$: C, 46.40; H, 4.50; N, 4.20%).

ν_{max}(film)/cm^{-1} 2962, 2925 (C-H), 1695 (C=O), 1363, 1172 (SO_2-N); δ_H(300MHz, $CDCl_3$) 7.91 (2H, d, *J*= 8.3, *H*Ar), 7.33 (2H, d, *J*= 8.3, *H*Ar), 6.10-5.97 (1H, m, C*H*=CH_2), 5.51-5.35 (2H, m, CH=C*H*$_2$), 5.02 (2H, d, *J*=5.5, C*H*$_2$), 2.45 (3H, s, C*H*$_3$$CCl_2$), 2.21 (3H, s, C*H*$_3$Ar); δ_C(75MHz, $CDCl_3$) 163.98 (*C*=O), 144.49 (*C*H=CH_2), 135.39, 132.82, 129.16 and 129.05 (4*C* of Ar), 119.01 (CH=*C*H_2), 79.67 (*C*Cl_2Me), 50.60 (*C*H_2), 35.62 (*C*H_3-CCl_2), 21.58 (*C*H_3); *m/z* (EI) 336 (M^+, 100%), 300 (73), 264 (80).

7.5.4.General procedure for the preparation of N-allyl-1-alkyl trichloroacetamides

Alkenylalcohol and MeONa (25% w/w) was stirred at 0°C in diethyl ether. Trichoroacetonitrile was added dropwise. The mixture was allowed to stirred at room temperature for 2 hours then washed with water and extracted with diethyl ether (3x50ml). The combined organic fractions were dried over magnesium sulfate and concentrated. The crude product was then refluxed in xylene (25ml) for 24 hours then concentrated. [91]

7.5.4.1. N-1-Methyl prop-2-enyl trichloroacetamide [179]

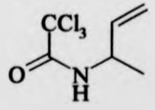


ν_{max}(film)/cm^{-1} 2962, 2925 (C-H), 1695 (C=O), 1363, 1172 (SO_2-N); δ_H(300MHz, $CDCl_3$) 7.91 (2H, d, *J*= 8.3, ***H***Ar), 7.33 (2H, d, *J*= 8.3, ***H***Ar), 6.10-5.97 (1H, m, C***H***=CH_2), 5.51-5.35 (2H, m, CH=C***H₂***), 5.02 (2H, d, *J*=5.5, C***H₂***), 2.45 (3H, s, C***H₃***CCl_2), 2.21 (3H, s, C***H₃***Ar); δ_C(75MHz, $CDCl_3$) 163.98 (***C***=O), 144.49 (***C***H=CH_2), 135.39, 132.82, 129.16 and 129.05 (4***C*** of Ar), 119.01 (CH=***C***H_2), 79.67 (***C***Cl_2Me), 50.60 (***C***H_2), 35.62 (***C***H_3-CCl_2), 21.58 (***C***H_3); ***m/z*** (EI) 336 (M^+, 100%), 300 (73), 264 (80).

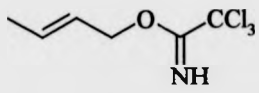
7.5.4.General procedure for the preparation of N-allyl-1-alkyl trichloroacetamides

Alkenylalcohol and MeONa (25% w/w) was stirred at 0°C in diethyl ether. Trichoroacetonitrile was added dropwise. The mixture was allowed to stirred at room temperature for 2 hours then washed with water and extracted with diethyl ether (3x50ml). The combined organic fractions were dried over magnesium sulfate and concentrated. The crude product was then refluxed in xylene (25ml) for 24 hours then concentrated. [91]

7.5.4.1. N-1-Methyl prop-2-enyl trichloroacetamide [179]



2-Buten-1-ol (5.4g, 75mmol) was reacted with trichoroacetonitrile (11g, 75mmol) and MeONa (25% w/w, 2g, 9.2mmol) in diethyl ether (50ml). The crude product [181] was collected as a light brown oil in 83% yield (13.40g).

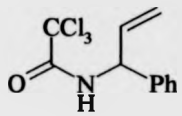


δ_H(250MHz, $CDCl_3$) 8.22 (1H, br, N***H***), 5.87-5.60 (2H, m, C***H***=C***H***), 4.65 (2H, d, *J*=5.1, CH_2), 1.71 (3H, d, *J*=6.9, CH_3); δ_C(62.5MHz, $CDCl_3$) 162.92 (***C***=N), 132.10, 124.73 (***C***H=***C***H), 70.25 (***C***Cl_3),56.75 (***C***H_2), 18.18 (***C***H_3).

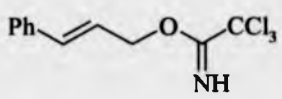
This crude product was then refluxed in xylene (25ml) for 24 hours then concentrated and purified by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) to afford the N-1-methyl prop-2-enyl trichloroacetamide [179] (3.05g, 61%) as a yellow solid; mp 39-42 °C. (Found: C, 33.78; H, 3.76; N, 4.45. Calc. for $C_6H_8NOCl_3$: C, 33.33; H, 3.75; N, 4.50%).

ν_{max}(film)/cm^{-1} 3333 (N-H), 1694 (C=O); δ_H(250MHz, $CDCl_3$) 6.63 (1H, br, N***H***), 5.89-5.77 (1H, m, C***H***=CH_2), 5.24-5.12 (2H, m, CH=CH_2), 4.57-4.42 (1H, m, C***H***), 1.31 (3H, d, *J*=6.7, CH_3); δ_C(62.5MHz, $CDCl_3$) 137.46 (***C***H=CH_2), 115.31 (CH=***C***H_2), 89.25 (***C***Cl_3), 60.18 (***C***HN), 19.49 (***C***H_3); *m/z* (EI) 216 (M^++1, 15%), 188 (100), 159 (98).

7.5.4.2. N-1-Phenyl-prop-2-enyl trichloroacetamide [180]



Cimanyl alcohol (5g, 37mmol) was reacted with trichoroacetonitrile (5.4g, 37mmol) and MeONa (25% w/w, 1g, 4.7mmol) in diethyl ether (50ml). The crude product [182] was collected (6.17g, 59%) as yellow oil.



δ_H(250MHz, $CDCl_3$) 8.29 (1H, br, s, N***H***), 7.39-7.21 (5H, m, ***H***-Ar), 6.70 (1H, d, *J*=15.8, Ph-C***H***=), 6.41-6.29 (1H, m, =C***H***-CH_2), 4.92 (2H, d, J=6.4, CH_2); δ_C(62.5MHz, $CDCl_3$) 163.26 (***C***=O), 135.91, 134.27, 128.34, 127.87, 126.44 and 122.11 (6***C*** of Ar and ***C***H=***C***H), 69.45 (***C***Cl_3), 56.12 (***C***H_2).

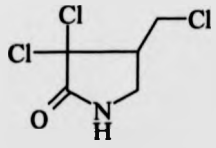
This crude product was then refluxed in xylene (25ml) for 24 hours then concentrated and purified by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) to afford the N-1-phenyl-prop-2-enyl trichloroacetamide [180] (2.03g, 33%) as a white solid; 44-46 °C. (Found: C, 47.56; H, 3.64; N, 4.90. Calc. for $C_{11}H_{10}NOCl_3$: C, 47.40; H, 3.60; N, 5.00%).

ν_{max}(film)/cm^{-1} 3286 (N-H), 1692 (C=O); δ_H(250MHz, $CDCl_3$) 7.44-7.25 (5H, m, *H*Ar), 6.98 (1H, br, N*H*), 6.12-5.99 (1H, m, C*H*=CH_2), 5.56 (1H, t, *J*=7.9, C*H*), 5.37-5.27 (2H, m, CH=CH_2); δ_C(62.5MHz, $CDCl_3$) 160.80 (*C*=O), 138.60, 135.42, 128.94, 128.22 and 126.98 (6*C* of Ar and *C*H=CH_2) 117.02 (CH=*C*H_2), 91.75 (*C*Cl_3), 56.91 (*C*H); *m/z* (EI) 278 (M^+, 55%), 242 (100), 206 (77), 115 (95).

7.5.5. General procedure for the cyclisation of N-allyl trichloroacetamide

The mixture of N-allyl trichloroacetamide and CuCl (30mol%) stirred under nitrogen for 30 minutes. Solvent was then added and solution of ligand (30mol%) in solvent (1 ml) was added immediately. The mixture was then heated to reflux for 24 hours. After cooling, the resulting mixture was eluted through a short silica gel column with dichloromethane. The γ-lactam was obtained as a white solid.

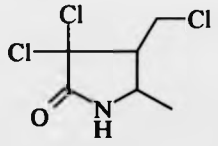
7.5.5.1. 4-Chloromethyl-3,3-dichloro pyrrolidin-2-one [175]



N-allyl trichloroacetamide (40mg, 0.19 mmol) in toluene (20ml) was reacted as described above to give 4-chloromethyl-3,3-dichloro pyrrolidin-2-one (30mg, 76%) as a white solid; mp 100-101 °C.

δ_H(250MHz, $CDCl_3$) 7.44 (1H, br, N***H***), 3.98 (1H, dd, *J*=11.25, 4.25, C***H***$_2$N), 3.78-3.66 (2H, m, 1H, of C***H***$_2$Cl and 1H of C***H***$_2$N), 3.27 (1H, t, *J*= 8.25, C***H***$_2$N), 3.22-3.10 (1H, m, C***H***); δ_C(62.5MHz, $CDCl_3$) 169.32 (***C***=O), 83.15 (***C***Cl_2), 53.70 (***C***HCl_2), 43.80 (***C***H_2N), 40.80 (***C***H_2Cl).

7.5.5.2. 4-Chloromethyl-3,3-dichloro-5-methyl pyrrolidin-2-one [183]

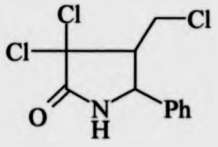


N-1-methylallyl trichloroacetamide (42mg, 0.19 mmol) in toluene (20ml) was reacted as described above to give 4-chloromethyl-3,3-dichloro-5-methyl pyrrolidin-2 (22mg, 52%) as a white solid, 90-92 °C.

δ_H(400MHz, $CDCl_3$) *trans* isomer, 7.42 (1H, br, N***H***), 4.00 (1H, dd, *J*=11.9, 5.3, C***H***$_2$Cl), 3.76 (1H, dd, *J*=11.9, 7.70, C***H***$_2$Cl), 3.61 (1H, dq, *J*= 14.0, 6.3, C***H***N), 2.73 (1H, dt, *J*= 7.7, 5.3, C***H***CCl_2), 1.48 (3H, d, *J*=9.7, C***H***$_3$), *cis* isomer 7.65 (1H, br, N***H***), 4.02-3.98 (2H, m, 1H of C***H***$_2$Cl and 1H of C***H***N), 3.79 (1H, t, *J*=11.2, C***H***$_2$Cl), 3.32-3.26 (1H, m, C***H***CCl_2), 1.38 (3H, d, *J*=11.2, C***H***$_3$); δ_C(100MHz, $CDCl_3$) 167.52

(*C*=O), 83.95 (*C*Cl_2), 61.11 (*C*HN), 52.00 (*C*HCCl_2), 39.80 *C*H_2Cl), 19.80 (*C*H_3); *m/z* (CI) 233 (M^++17, 87%), 163 (92), 129 (100).

7.5.5.3. 4-Chloromethyl-3,3-dichloro-5-phenyl pyrrolidin-2-one [184]



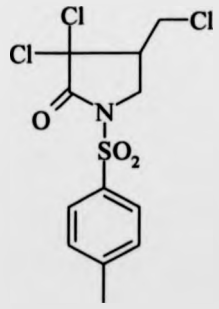
N-1-phenylallyl trichloroacetamide (55mg, 0.19 mmol) in toluene (20ml) was reacted as described above to give 4-chloromethyl-3,3-dichloro-5-phenyl pyrrolidin-2-one (26mg, 50%) as a white solid; mp 160-161 °C.

δ_H(400MHz, $CDCl_3$) *trans* isomer, δ: 7.42-7.34 (5H, m, ***H***-Ar), 6.46 (1H, br, N***H***), 4.41 (1H, d, *J*=8.2, C***H***Ph), 4.01 (1H, dd, *J*=11.9, 7.3, CH_2Cl), 3.72 (1H, dd, *J*= 11.9, 5.8, CH_2Cl), 3.10-3.01 (1H, dt, *J*= 7.7, 5.2, C***H***CCl_2), *cis* isomer, δ: 7.42-7.34 (5H, m, ***H***-Ar), 6.46 (1H, br, N***H***), 5.40, (1H, dd, *J*=7.9, 1.8, C***H***Ph), 4.09 (1H, dd, *J*=13.1, 7.3, CH_2Cl), 3.72 (1H, dd, *J*= 13.1, 5.8, CH_2Cl), 3.10-3.01 (1H, dt, *J*= 7.7, 5.2, C***H***CCl_2); δ_C(100MHz, $CDCl_3$) 167.20 (***C***=O), 136.20, 129.56, 129.26 and 126.94 (6***C*** of Ar), 83.25 (***C***Cl_2), 61.56 (***C***HN), 59.38 (***C***HCCl_2), 39.05 (***C***H_2Cl); ***m/z*** (EI) 278 (M^+, 19%), 242 (97), 208 (100), 199 (99).

7.5.6. General procedure for the cyclisation of N-allyl-N-tosyl trihaloacetamide

N-allyl-tosyl trichloroacetamide and CuCl (30mol%) were stirred under nitrogen for 30 minutes. Solvent was then added and solution of ligand (30mol%) in solvent (1ml) was added immediately. The mixture was stirred for 2 hours at room temperature. The resulting mixture was eluted through a short silica gel column with dichlorometane. The γ-lactam was obtained as a white solid.

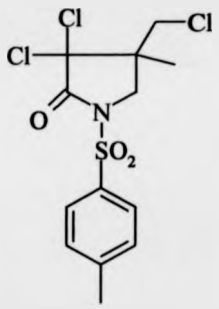
7.5.6.1. 4-Chloromethyl-3,3-dichloro-1-tosyl pyrrolidin-2-one [173]



N-allyl-tosyl trichloroacetamide (231mg, 0.65 mmol) in toluene (5ml) was reacted as described above to give 4-chloromethyl-3,3-dichloro-1-tosyl pyrrolidin-2-one (30mg, 99%) as a white solid; mp 160-162 °C.

ν_{max}(film)/cm^{-1} 2923, 2852 (C-H), 1658 (C=O); δ_H(250MHz, $CDCl_3$) 7.92 (2H, d, *J*=8.2, ***H***-Ar), 7.36 (2H, d, *J*=8.2, ***H***-Ar), 4.24 (1H, dd, *J*=10.3, 7.0, C***H***$_2$N), 3.92 (1H, dd, *J*=11.6, 4.3, C***H***$_2$Cl),3.65 (1H, dd, *J*=11.6, 9.8, C***H***$_2$Cl) 3.55 (1H, dd, *J*= 10.3, 8.4, C***H***$_2$N), 3.10-3.03 (1H, m, C***H***), 2.45 (3H, s, C***H***$_3$Ar); δ_C(62.5MHz, $CDCl_3$) 162.90 (***C***=O), 146.30, 133.20, 129.93 and 128.16 (6***C*** of Ar), 82.48 (***C***Cl_2), 50.59 (***C***H_2N), 47.33 (***C***H), 40.02 (***C***H_2Cl), 21.68 (***C***H_3).

7.5.6.2. 4-Chloromethyl-3,3-dichloro-4-methyl-1-tosyl pyrrolidin-2-one [177b]

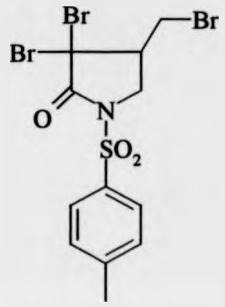


N-2-methylallyl-tosyl trichloroacetamide (73mg, 0.19 mmol) in toluene (20ml) was reacted as described above to give 4-chloromethyl-3,3-dichloro-4-methyl-1-tosyl pyrrolidin-2-one (60mg, 88%) as a white solid; mp 125-126 °C.

ν_{max}(film)/cm^{-1} 1680 (C=O); δ_H(250MHz, $CDCl_3$) 7.90 (2H, d, *J*=8.2, ***H***-Ar), 7.35 (2H d, *J*=8.2, ***H***-Ar), 3.94 (1H, d, *J*=10.3, C***H***$_2$N), 3.68 (1H, d, *J*=10.3, C***H***$_2$N), 3.60 and 3.50 (2H, d, 11.6, C***H***$_2$Cl), 2.44 (3H, s, C***H***$_3$Ar), 1.33 (3H, s, C***H***$_3$Cl); δ_C(62.5MHz,

$CDCl_3$) 162.97 (*C*=O), 146.15, 133.33, 129.86 and 128.02 (6*C* of Ar), 88.07 (CCl_2), 52.30 (CH_2N), 49.19 (CCH_3), 46.72 (CH_2Cl), 21.68 (CH_3), 18.08 (CH_3C); *m/z* (EI) 369 (M^+, 10%), 316 (81), 279 (100).

7.5.6.3. 4-Bromomethyl-3,3-dibromoro-1-tosyl pyrrolidin-2-one [192]

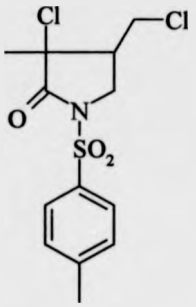


N-allyl-tosyl tribromoacetamide (96mg, 0.20 mmol) in toluene (20ml) was reacted as described above to give 4-bromomethyl-3,3-dibromo-4-methyl-1-tosyl pyrrolidin-2-one (83mg, 87%) as a white solid; mp 98-99 °C. (Found: C, 29.69; H, 2.25; N, 2.30. Calc. for $C_{12}H_{13}NO_3SBr_3$: C, 29.35; H, 2.67; N, 2.85%). (Found M+ 487.4189, $C_{12}H_{13}NO_3SBr_3$ requires 487.4185).

ν_{max}(film)/cm^{-1} 1594 (C=O); δ_H(250MHz, $CDCl_3$) 7.92 (2H, d, *J*=8.4, *H*-Ar), 7.36 (2H, d, *J*=8.4, *H*-Ar), 4.17 (1H, dd, *J*=10.3, 7.0, CH_2N), 3.74 (1H, dd, *J*=11.6, 4.3, CH_2Br), 3.47-3.40 (2H, m, 1H of CH_2Br and 1H of CH_2N), 3.04-2.96 (1H, m, C*H*), 2.45 (3H, s, CH_3); δ_C(62.5MHz, $CDCl_3$) 163.45 (*C*=O), 146.20, 132.95, 129.87 and

128.09 (6*C* of Ar), 58.92 (*C*Br_2), 51.60 (*C*H_2N), 49.23 (*C*H), 28.40 (*C*H_2Br), 21.68 (*C*H_3); *m/z* (EI) 490 (M^+, 64%), 410 (67), 345 (81), 149 (100).

7.5.6.4. 3-Chloro-4-chloromethyl-3-methyl-1-tosyl pyrrolidin-2-one [50]

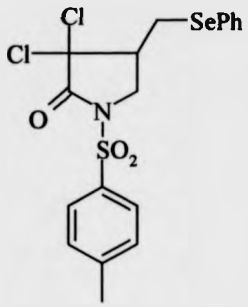


N-allyl-N-tosyl dichloromethylacetamide (73mg, 0.19 mmol) in toluene (20ml) was reacted as described above to give 4-chloromethyl-3,3-dichloro-4-methyl-1-tosyl pyrrolidin-2-one (60mg, 88%) as a white solid; mp 110-111 °C.

ν_{max}(film)/cm^{-1} 1596 (C=O); δ_H(300MHz, $CDCl_3$) *trans* isomer; 7.83 (2H, d, *J*=8.2, ***H***-Ar), 7.28 (2H, d, *J*=8.2, ***H***-Ar), 4.14 (1H, dd, *J*=10.0, 6.9, C***H***$_2$N), 3.70 (1H, dd, *J*=11.5, 5.4, C***H***$_2$Cl), 3.56 (1H, dd, *J*=9.0, 6.4, C***H***$_2$Cl), 3.36 (1H, t, *J*=9.8, C***H***$_2$N), 2.38 (3H, s, C***H***$_3$Ar), 1.65 (3H, s, C***H***$_3$CCl), *cis* isomer; 7.83 (2H, d, *J*=8.2, ***H***-Ar), 7.28 (2H, d, *J*=8.2, ***H***-Ar), 4.07 (1H, dd, *J*=10.9, 6.6, C***H***$_2$N), 3.80 (1H, dd, *J*=11.2, 3.6, C***H***$_2$Cl), 3.61 (1H, dd, *J*=11.2, 4.3, C***H***$_2$Cl), 3.34 (1H, t, *J*=10.9, C***H***$_2$N), 2.38 (3H, s, C***H***$_3$Ar), 1.52 (3H, s, C***H***$_3$CCl); δ_C(75MHz, $CDCl_3$) 169.12 (*C*=O), 146.29, 132.15, 130.24 and 128.49 (6*C* of Ar), 69.37 (*C*Cl), 48.13 and 47.73 (*C*H_2N), 47.43

and 47.19 (*C*H), 42.28 and 41.38 (*C*H_2Cl), 24.24 and 22.17 (*C*H_3C), 21.08 (*C*H_3Ar); *m/z* (EI) 336 (M^+, 19%), 217 (100), 236 (20), 210 (74).

7.5.6.5. 4-Benzeneselenomethyl-3,3-dichloro-1-tosyl pyrrolidin-2-one [189]



N-allyl-tosyl trichloroacetamide (70mg, 0.19 mmol), diphenyl diselenide (183mg, 59mmol) and CuCl (8.4 mg, 30mol%) were stirred under nitrogen for 30 minutes. Toluene (19ml) was then added and solution of ligand (10.6mg, 30mol%) in toluene (1ml) was added immediately. The mixture was stirred for 74 hours at room temperature. The resulting mixture was eluted through a short silica gel column with dichlorometane. Benzeneselenomethyl-3,3-dichloro-4-methyl-1-tosyl pyrrolidin-2-one (16mg, 24%) as a light yellow oil.

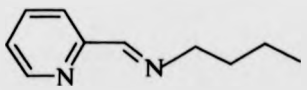
δ_H(250MHz, $CDCl_3$) 7.87 (2H, d, *J*=8.0, *H*-Ar), 7.53-7.51 (2H, m, *H*-Ar), 7.35-7.31 (6H, m, *H*-Ar), 4.19 (1H, dd, *J*=11.4, 7.0, CH_2N), 3.40-3.34 (2H, m, CH_2Se) 2.87 (1H, dd, *J*= 11.4, 10.9, CH_2N), 2.80-2.44 (1H, m, C*H*), 2.44 (3H, s, CH_3), δ_C(62.5MHz,

$CDCl_3$) 163.50 (*C*=O), 146.10, 133.04, 129.83 and 128.11 (6*C* of Ar), 100.54 (CCl_2), 49.30 (CH_2N), 48.65 (*C*H), 23.08 (CH_3); *m/z* (EI) 477 (M^+, 100%), 167 (47), 65 (72).

7.5.7. General procedure for the preparation of N-allyl-2-pyridylmethanimine

Alkylamine (1eq) was added to a solution of 2-pyridine carbaldehyde (1 eq) in diethyl ether (20ml). The solution was stirred at room temperature for 10 minutes and a large excess of magnesium sulfate (20g) was added. This suspension was left for 2 hours to remove all the water produced from the reaction. The diethyl ether was removed under reduced pressure to give a yellow liquid which was then purified by vacuum distillation (15mmHg).

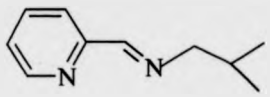
7.5.7.1. N-(n-Butyl)-2-pyridylmethanimine [195]



n-Butylamine (7g, 93 mmol) was reacted with 2-pyridine carbaldehyde (10g, 93 mmol) to afford N-(n-butyl)-2-pyridylmethanimine(10.97mg, 73%) as a light yellow oil.(Found M+ 162.1158, $C_{10}H_{14}N_2$ requires 162.1157).

ν_{max}(film)/cm^{-1} 1649 (C=N), 1585, 1566, 1467 (C=C); δ_H(300MHz, $CDCl_3$) 8.43 (1H, d, *J*= 3.7, ***H***-Ar), 8.18 (1H, s, ***H***C=N), 7.79 (1H, d, *J*=7.7, ***H***-Ar), 7.50 (1H, t, *J*= 7.7, ***H***-Ar), 7.52 (1H, t, *J*=7.7, ***H***-Ar), 3.47 (2H, t, *J*=6.8, C***H***$_2$-N), 1.55-1.46 (2H, m, C***H***$_2$-CH_2N), 1.25-1.16 (2H, m, C***H***$_2$), 0.74 (3H, t, *J*= 7.3, C***H***$_3$); δ_C(75MHz, $CDCl_3$) 161.80, 154.91, 149.56, 136.60, 124.71 and 121.32 (5***C*** of Ar and ***C***H=N), 61.42 (***C***H_2-N), 32.98and 20.62 (2 x ***C***H_2), 14.08 (***C***H_3); *m/z* (EI) 162 (M^+, 10%), 119 (100), 92 (45), 57 (38).

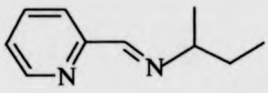
7.5.7.2. N-(iso-Butyl)-2-pyridylmethanimine [196]



iso-Butylamine (7g, 93 mmol) was reacted with 2-pyridine carbaldehyde (10g, 93 mmol) to afford N-(iso-butyl)-2-pyridylmethanimine (9.26g, 62%) as a light yellow oil. (Found M+ 162.1157, $C_{10}H_{14}N_2$ requires 162.1157).

ν_{max}(film)/cm^{-1} 1649 (C=N), 1587, 1567, 1469 (C=C); δ_H(300MHz, $CDCl_3$) 8.18 (1H, d, *J*= 3.0, ***H***-Ar), 7.90 (1H, s, ***H***C=N), 7.56 (1H, d, *J*=7.7, ***H***-Ar), 7.25 (1H, t, *J*= 7.7, ***H***-Ar), 6.82 (1H, t, *J*=7.7, ***H***-Ar), 3.04 (2H, d, *J*=6.6, C***H***$_2$-N), 1.66-1.52 (1H, m, C***H***-CH_3), 0.54 and 0.51 (6H, d, *J*=6.7, 2 x C***H***$_3$), 0.74 (3H, t, *J*= 3.5, C***H***$_3$); δ_C(75MHz, $CDCl_3$) 161.95, 154.93, 149.53, 136.58, 124.71 and 121.28 (5***C*** of Ar and ***C***H=N), 69.70 (***C***H_2-N), 29.66 (***C***H), 20.89 (2 x ***C***H_3); *m/z* (CI) 163 (M^++1, 62%) 119 (30), 35 (100).

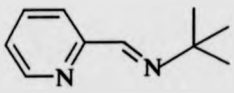
7.5.7.3. N-(sec-Butyl)-2-pyridylmethanimine [197]



sec-Butylamine (7g, 93 mmol) was reacted with 2-pyridine carbaldehyde (10g, 93 mmol) to afford N-(sec-butyl)-2-pyridylmethanimine (10.12g, 68%) as a light yellow oil. (Found M+ 162.1135, $C_{10}H_{14}N_2$ requires 162.1157).

ν_{max}(film)/cm^{-1} 1647 (C=N), 1587, 1566, 1467 (C=C); δ_H(300MHz, $CDCl_3$) 7.97 (1H, d, *J*= 4.6, ***H***-Ar), 7.74 (1H, s, ***H***C=N), 7.37 (1H, d, *J*=7.2, ***H***-Ar), 7.01 (1H, t, *J*= 7.2, ***H***-Ar), 6.57 (1H, t, *J*=7.2, ***H***-Ar), 2.65-2.57 (1H, m, C***H***-N), 1.02-0.93 (2H, m, C***H₂***-CH_3), 0.62 (3H, d, *J*=6.4, C***H₃***-CH), 0.21 (3H, t, *J*= 7.3, C***H₃***); δ_C(75MHz, $CDCl_3$) 161.57, 156.44, 150.87, 137.83, 125.97 and 122.78 (5***C*** of Ar and ***C***H=N), 69.30 (***C***H-N), 32.13 (***C***H_2), 23.78 and 12.57 (2 x ***C***H_3); *m/z* (CI) 163 (M^++1, 90%) 133 (29) 35 (100).

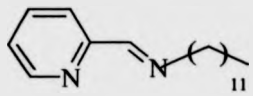
7.5.7.4. N-(tert-Butyl)-2-pyridylmethanimine [198]



tert-Butylamine (3.4g, 47mmol) was reacted with 2-pyridine carbaldehyde (5g, 47mmol) to afford N-(tert-butyl)-2-pyridylmethanimine (4.13g, 55%) as a light yellow oil. (Found M+ 162.1153, $C_{10}H_{14}N_2$ requires 162.1157)

ν_{max}(film)/cm^{-1} 1714 (C=N), 1644, 1586, 1467 (C=C); δ_H(300MHz, $CDCl_3$) 8.38 (1H, d, *J*= 4.70, ***H***-Ar), 8.13 (1H, s, ***H***C=N), 7.79 (1H, d, *J*=6.95, ***H***-Ar), 7.45 (1H, t, *J*= 7.75, ***H***-Ar), 7.02 (1H, t, *J*=6.20, ***H***-Ar), 1.08 (9H, s, 3x C***H₃***); δ_C(75MHz, $CDCl_3$) 156.48, 149.38, 136.59, 124.55 and 121.08 (5***C*** of Ar and ***C***H=N), 57.92 (***C***-N), 29.75 (3 x ***C***H_3); ***m/z*** (CI) 163 (M^++1, 27%), 108 (24), 35 (100).

7.5.7.5. N-Dodecyl-2-pyridylmethanimine [199]



n-Dodecylamin (8.65g, 93 mmol) was reacted with 2-pyridine carbaldehyde (10g, 93 mmol) to afford N-dodecyl-2-pyridylmethanimine (4.75g, 37%) as a light yellow oil. (Found M+ 274.2405, $C_{18}H_{31}N_2$ requires 274.2409).

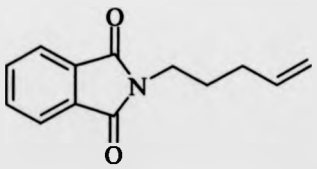
ν_{max}(film)/cm^{-1} 1649 (C=N), 1584, 1566, 1466 (C=C); δ_H(300MHz, $CDCl_3$) 8.60 (1H, d, *J*= 3.9, ***H***-Ar), 8.34 (1H, s, ***H***C=N), 7.95 (1H, d, *J*=7.2, ***H***-Ar), 7.69 (1H, t, *J*= 7.2, ***H***-Ar), 7.25 (1H, t, *J*=7.2, ***H***-Ar), 3.64 (2H, t, *J*=6.9, C***H₂***-N), 1.71-1.64 (2H, m, C***H₂***-CH_2N), 1.30-1.22 (18H, m, 9x C***H₂***), 0.84 (3H, t, *J*= 6.6, C***H₃***); δ_C(75MHz, $CDCl_3$) 161.98, 155.03, 149.72, 136.82, 124.89 and 121.50 (5***C*** of Ar and ***C***H=N), 61.96 (***C***H_2-N), 34.26, 32.27, 31.05, 29.99, 29.95, 29.79, 29.71, 27.69 and 23.04 (10 x ***C***H_2), 14.48 (***C***H_3); ***m/z*** (EI) 274 (M^+, 21%), 218 (48), 119 (100), 92 (42).

7.6. Experimental for chapter 6

7.6.1. General procedure for the preparation of N-alkenyl-phthalimide

Potassium phthalimide and alkenyl bromide were stirred in N-N-dimethylformamide at 100 °C for 3 hours. The crude mixture was diluted with water and the product extracted into diethyl ether. The extracts were washed with water (3 x 30ml), dried and evaporated to dryness. [103]

7.6.1.1. N-(Pent-4-enyl)phthalimide [210a]

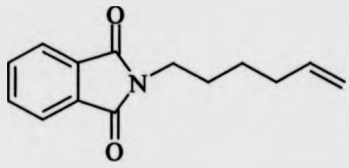


5-Bromo-1-pentene (3g, 20mmol) was reacted with potassium phthalimide (4g, 22mmol) in N-N-dimethylformamide (20ml) to afford N-(pen-4-eyl)phthalimide (3.52g, 82%) as a white solid which was used further without purification.

ν_{max}(film)/cm^{-1} 1776 (C=O), 1642, 1615 (C=C); δ_H(300MHz, $CDCl_3$) 7.77-7.74 and 7.64-7.61 (4H, m, ***H***-Ar), 5.80-5.67 (1H, m, C***H***=CH_2), 5.02-4.87 (2H, m, CH=C***H***$_2$), 3.62 (2H, t, J = 7.1, C***H***$_2$-N), 2.03, (2H, q, J= 7.0, C***H***$_2$-CH=), 1.71 (2H, m, C***H***$_2$),

δ_C(75MHz, $CDCl_3$) 168.78, (*C*=O), 137.69 (*C*H=CH_2), 134.25, 132.51 and 123.54 (6*C* of Ar), 115.67 (CH=*C*H_2), 37.93, 31.36 and 28.00 (3x *C*H_2); *m/z* (CI) 216 (M^++1, 88%), 160 (100), 104 (44), 76 (18).

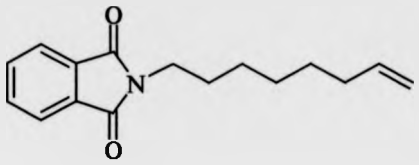
7.6.1.2. N-(Hex-5-enyl)phthalimide [210b]



6-Bromo-1-hexene (1g, 6.1mmol) was reacted with potassium phthalimide (1.2g, 6.5mmol) in N-N-dimethylformamide (10ml) to afford N-(hex-5-eyl)phthalimide in 60% yield (0.85g) as a white solid which was used further without purification.

ν_{max}(film)/cm^{-1} 1770 (C=O), 1641, 1998 (C=C); δ_H(300MHz, $CDCl_3$) 7.78-7.75 and 7.65-7.62 (4H, m, *H*-Ar), 5.77-5.64 (1H, m, C*H*=CH_2), 4.96-4.84 (2H, m, CH=C*H*$_2$), 3.62 (2H, t, *J* = 7.0, C*H*$_2$-N), 2.02, (2H, q, *J*= 7.0, C*H*$_2$-CH=), 1.67-1.53 and 1.42-1.32 (4H, m, 2xC*H*$_2$); δ_C(75MHz, $CDCl_3$) 168.83, (*C*=O), 138.65 (*C*H=CH_2), 134.24, 132.52 and 123.54 (6*C* of Ar), 115.25 (CH=*C*H_2), 38.23, 33.62, 28.41 and 26.45 (4x *C*H_2); *m/z* (CI) 230 (M^++1, 62%), 160 (100), 76 (37).

7.6.1.3. N-(Oct-7-enyl)phthalimide [210c]



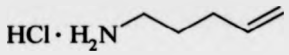
8-Bromo-1-octene (1g, 5.2mmol) was reacted with potassium phthalimide (1g, 5.4mmol) in N-N-dimethylformamide (10ml) to afford N-(oct-4-enyl)phthalimide (1.12g, 83%) as a light yellow viscous oil which was used further without purification.

ν_{max}(film)/cm^{-1} 1772 (C=O), 1640, 1597 (C=C); δ_H(300MHz, $CDCl_3$) 7.93-7.72 (2H, m, ***H***-Ar), 7.64-7.62 (2H, m, ***H***-Ar), 5.77-5.63 (1H, m, C***H***=CH_2), 4.83-4.81 (2H, m, CH=C***H$_2$***), 3.59 (2H, t, J = 7.3, C***H$_2$***-N), 1.95-1.91 (2H, m, C***H$_2$***-CH=), 1.61-1.32 (2H, m, C***H$_2$***), 1.28-1.24 (6H, m, 3xC***H$_2$***); δ_C(75MHz, $CDCl_3$) 168.79, (***C***=O), 137.28 (***C***H=CH_2), 134.46, 132.49 and 123.48 (6***C*** of Ar), 114.64 (CH=***C***H$_2$), 38.35, 36.84, 34.00, 31.77, 28.54 and 27.04 (6x ***C***H$_2$); ***m/z*** (CI) 258 (M^++1, 100%), 160 (61), 110 (45), 83 (42).

7.6.2. General procedure for the preparation of alkenylamine hydrochloride

A solution of hydrazine hydrate (2eq.) and N-alkenyl phthalimide (1eq.) in ethanol was refluxed for 24 hours. The white precipitate of phthalhydrazide was filtrered and concentrated HCl was added dropwise to the filtrate. The resulted suspension was concentrated under vacuum to remove all solvent and water. [103]

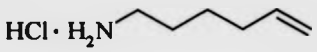
7.6.2.1. Pent-4-enylamine hydrochloride [211a]



N-(Pent-4-enyl)phthalimide (1g, 4.65mmol) was reacted with hydrazine hydrate (0.3g, 9.4mmol) in ethanol (20ml) to afford pente-4-nylamine hydrochloride (290mg, 51%) as a white solid which was used without further purification.

ν_{max}(film)/cm^{-1} 3320 (N-H), 1644 (C=C); δ_H(300MHz, $CDCl_3$) 8.30 (2H, br, NH_2), 5.85-5.70 (1H, m, CH=CH_2), 5.12-5.01 (2H, m, CH=CH_2), 3.11-2.93 (2H, m, CH_2-N), 2.25-2.12 (2H, m, CH_2-CH=), 1.97-1.85 (2H, m, CH_2); δ_C(75MHz, $CDCl_3$) 136.51 (CH=CH_2), 116.94 (CH=CH$_2$), 39.73, 30.79 and 26.98 (3 x CH$_2$).

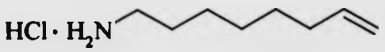
7.6.2.2. Hex-5-enylamine hydrochloride [211b]



N-(Hex-5-enyl)phthalimide (0.4g, 1.7mmol) was reacted with hydrazine hydrate (0.11g, 3.4mmol) in ethanol (20ml) to afford Hexe-5-nylamine hydrochloride (150mg, 65%) as a white solid which was used without further purification.

ν_{max}(film)/cm^{-1} 3400 (N-H), 1662 (C=C); δ_H(300MHz, $CDCl_3$) 8.32 (2H, br, N***H*****$_2$**), 5.86-5.73 (1H, m, C***H***=CH_2), 5.08-4.95 (2H, m, CH=C***H*****$_2$**), 3.01-2.90 (2H, m, C***H*****$_2$**-N), 2.15-2.08 (2H, m, C***H*****$_2$**-CH=), 1.85-1.66 and 158-1.44 (4H, m, 2x C***H*****$_2$**), δ_C(75MHz, $CDCl_3$) 137.98 (***C***H=CH_2), 112.28 (CH=***C***H_2), 40.21, 33.29, 27.41 and 26.04 (4 x ***C***H_2).

7.6.2.3. Oct-7-enylamine hydrochloride [211c]



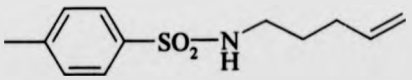
N-(Oct-7-enyl)phthalimide (0.94g, 3.6mmol) was reacted with hydrazine hydrate (0.23g, 7.3mmol) in ethanol (20ml) to afford octe-7-nylamine hydrochloride (325mg, 55%) as a white solid which was used without further purification.

ν_{max}(film)/cm^{-1} 3370 (N-H), 1660 (C=C); δ_H(300MHz, $CDCl_3$) 8.27 (2H, br, NH_2), 5.87-5.73 (1H, m, CH=CH_2), 5.04-4.94 (2H, m, CH=CH_2), 3.00-2.90 (2H, m, CH_2-N), 2.07-2.02 (2H, m, CH_2-CH=), 1.79-1.70 (2H, m, CH_2), 1.47-1.30 (4H, m, 2x CH_2); δ_C(75MHz, $CDCl_3$) 139.11 (*C*H=CH_2), 114.92 (CH=*C*H_2), 40.36, 33.96, 28.95, 28.79, 27.98, and 26.72 (6 x *C*H_2).

7.6.3.General procedure for the preparation of N-alkenyl-N-tosylamides

Triethylamine (2 eq.) was added dropwise to a stirred suspension of *p*-toluenesulphonyl chloride (1 eq.) and alkenylamine hydrochloride (1 eq.) in THF at room temperature. The mixture was allowed to stir at this temperature for 4 hours. The resulting solution was then concentrated, taken up in water, extracted with diethyl ether, dried over magnesium sulfate and concentrated.

7.6.3.1. N-Pent-4-enyl-N-tosylamide [212a]

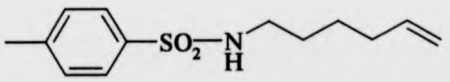


Pent-4-enylamine hydrochloride (0.28mg, 2.3mmol) was reacted with *p*-toluenesulphonyl chloride (0.46g, 2.4mmol) and triethylamine (0.5g, 4.8mmol) in THF (20 ml). Purification by silica gel column chromatography (petroleum ether:

ethyl acetate, 5:1) afforded N-pent-4-enyl-N-tosylamide (500mg, 90%) as white solid; mp 95-96 °C. (Found: C, 60.45; H, 7.02; N, 5.80. Calc. for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85%). (Found M+ 239.1002, $C_{12}H_{17}NO_2S$ requires 239.0997).

ν_{max}(film)/cm^{-1} 3279 (N-H), 1641, 1598, 1495 (C=C); δ_H(300MHz, $CDCl_3$) 7.73 (2H, d, *J*=8.2, ***H***-Ar), 7.27 (2H, d, *J*=8.2, ***H***-Ar), 5.71-5.61 (1H, m, C***H***=CH_2), 5.06 (1H, br, N***H***), 4.94-4.88 (2H, m, CH=C***H₂***), 2.89 (2H, t, *J*=7.0, C***H₂***-N), 2.39 (3H, s, C***H₃***), 2.02-1.97 (2H, m, C***H₂***-CH=), 1.56-1.49 (2H, m, C***H₂***), δ_C(75MHz, $CDCl_3$) 143.73 (1***C*** of Ar), 137.66 (***C***H=CH_2), 137.34, 130.08 and 127.48 (3***C*** of Ar), 115.90 (CH=***C***H_2), 42.00, 31.03 and 29.04 (3C of ***C***H_2), 21.90 (***C***H_3); ***m/z*** (CI) 240 (M^++1, 30%), 184 (65), 155 (100), 91 (94).

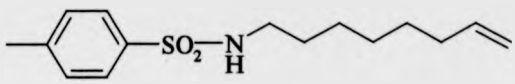
7.6.3.2. N-Hex-5-enyl-N-tosylamide [212b]



Hex-5-enylamine hydrochloride (133mg, 0.98mmol) was reacted with *p*-toluenesulphonyl chloride (187mg, 0.98mmol) and triethylamine (202mg, 2mmol) in THF (20 ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-hex-5-enyl-N-tosylamide in 85% yield (211mg) as white solid; mp 94-95 °C. (Found: C, 61.73; H, 7.40; N, 5.82. Calc. for $C_{13}H_{19}NO_2S$: C, 61.63; H, 7.56; N, 5.53%). (Found M+ 253.1160, $C_{13}H_{19}NO_2S$ requires 253.1153).

ν_{max}(film)/cm^{-1} 3278 (N-H), 1644, 1597, 1495 (C=C); δ_H(300MHz, $CDCl_3$) 7.77 (2H, d, *J*=8.1, ***H***-Ar), 7.30 (2H, d, *J*=8.1, ***H***-Ar), 5.76-5.63 (1H, m, C***H***=CH_2), 5.18 (1H, br, t, *J*= 5.6, N***H***), 4.96-4.88 (2H, m, CH=C***H₂***), 2.90 (2H, q, *J*=6.4, C***H₂***-N), 2.41 (3H, s, C***H₃***), 1.95 (2H, q, *J*= 6.6, C***H₂***-CH=), 1.49-4.41 and 1.37-1.31 (2H, m, C***H₂***); δ_C(75MHz, $CDCl_3$) 143.65 (1***C*** of Ar), 138.57 (***C***H=CH_2), 137.34, 130.06 and 127.48 (3***C*** of Ar), 115.15 (CH=***C***H_2), 43.40, 33.45, 29.26 and 26.07 (4C of ***C***H_2), 21.88 (***C***H_3); *m/z* (CI) 254 (M^++1, 52%), 184 (62), 155 (92), 91 (100).

7.6.3.3. N-Oct-7-enyl-N-tosylamide [212c]

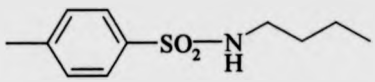


Oct-7-enylamine hydrochloride (0.28g, 1.7mmol) was reacted with *p*-toluenesulphonyl chloride (0.32g, 1.7mmol) and triethylamine (0.34g, 3.4mmol) in THF (20 ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-oct-7-enyl-N-tosylamide (432mg, 92%) as white solid; mp 65-66 °C. (Found: C, 64.39; H, 8.04; N, 5.30. Calc. for $C_{15}H_{23}NO_2S$: C, 64.02; H, 8.24; N, 4.98%). (Found M+, 281.1458, $C_{15}H_{23}NO_2S$ requires 281.1466).

ν_{max}(film)/cm^{-1} 3280 (N-H), 1640, 1598, 1494 (C=C); δ_H(300MHz, $CDCl_3$) 7.66 2H, d, *J*=8.3, ***H***-Ar), 7.20 (2H, d, *J*=8.3, ***H***-Ar), 5.70-5.59 (1H, m, C***H***=CH_2), 5.18 (1H, br, N***H***), 4.90-4.79 (2H, m, CH=C***H₂***), 2.80 (2H, q, *J*=6.6, C***H₂***-N), 2.32 (3H, s, C***H₃***), 1.88 (2H, q, *J*= 7.3, C***H₂***-CH=), 1.36-1.29 (2H, m, C***H₂***), 1.22-1.10 (6H, m, 3x C***H₂***);

δ_C(75MHz, $CDCl_3$) 143.27 (1*C* of Ar), 138.64 (*C*H=CH_2), 136.76, 29.426 and 126.86 (5*C* of Ar), 114.06 (CH=*C*H_2), 42.93, 33.35, 29.18, 28.40, 28.26 and 26.09 (6C of *C*H_2), 21.26 (*C*H_3); *m/z* (EI) 282 (M^++1, 11%), 184 (66), 155 (100), 91 (94).

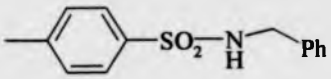
7.6.3.4. N-(n-butyl)-N-tosylamide [212d]



n-Butylamine (4.06g, 56mmol) was reacted with *p*-toluenesulphonyl chloride (5.30g, 28mmol) in THF (50 ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-(n-butyl)-N-tosylamide (4.85g, 82%) as white solid; mp 99-100 °C. (Found: C, 57.82; H, 7.35; N, 6.03. Calc. for $C_{11}H_{17}NO_2S$: C, 58.12; H, 7.54; N, 6.16%). (Found M+, 227.0993 $C_{11}H_{17}NO_2S$ requires 227.0997).

ν_{max}(film)/cm^{-1} 3581 (N-H), 1598, 1495 (C=C); δ_H(300MHz, $CDCl_3$) δ: 7.76 (2H, d, *J*=8.4, *H*-Ar), 7.29 (2H, d, *J*=8.4, *H*-Ar), 5.15 (1H, br, N*H*), 2.92-2.87 (2H, m, CH_2-N), 2.41 (3H, s, CH_3-Ar), 145-1.33 and 1.30-1.21 (2H, m, 2x CH_2), 0.82 (3H, t, *J*=7.3, CH_3); δ_C(75MHz, $CDCl_3$) 143.61 137.35, 130.03 and 127.47 (6*C* of Ar), 43.27 (*C*H_2-N), 31.86 (*C*H_2), 21.86 (*C*H_3-Ar), 20.06 (*C*H_2), 13.90 (*C*H_3); *m/z* (EI) 227 (M^+, 14%), 184 (75), 155 (100), 91 (89).

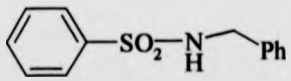
7.6.3.5. N-Benzyl-N-tosylamide



Benzylamine (0.6g, 5.6mmol) was reacted with *p*-toluenesulphonyl chloride (1g, 5.3mmol) and triethylamine (0.6g, 5.9mmol) in THF (30 ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-benzyl-N-tosylamide (1.26g, 91%) as white solid, mp 125-126 °C. (Found: C,64.68 ; H, 5.65; N, 5.00. Calc. for $C_{14}H_{15}NO_2S$: C, 64.34; H, 5.78; N, 5.36%). (Found M+, 261.0844 $C_{14}H_{15}NO_2S$ requires 261.0840).

ν_{max}(film)/cm^{-1} 3410 (N-H), 1670, 1553 (C=C); δ_H(300MHz, $CDCl_3$) 7.67 (2H, d, *J*=8.3, ***H***-Ar), 7.25-7.10 (8H, m, ***H***-Ar), 4.64 (1H, br, N***H***), 4.04 (2H, d, *J*=6.2, CH_2), 2.37 (3H, s, CH_3); δ_C(75MHz, $CDCl_3$) 143.95, 137.01, 136.64, 130.15, 129.10, 128.32, 128.27 and 127.59 (***C*** of 2Ar), 47.67 (***C***H_2), 21.94 (***C***H_3); ***m/z*** (EI) 261 (M^+, 10%), 106 (100), 91 (82).

7.6.3.6. N-Benzyl-N-benzenesulfonylamide



Benzylamine (0.6g, 5.6mmol) was reacted with benzenesulfonyl chloride (1g, 5.6mmol) and triethylamine (0.57g, 5.6mmol) in THF (20 ml). Purification by silica

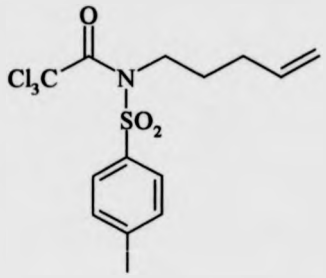
gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-Benzyl-N-benzenesulfonylamide (880mg, 63%) as white solid; mp 120-121 °C. (Found: C, 63.46; H, 5.23; N, 5.38. Calc. for $C_{13}H_{13}NO_2S$: C, 63.13; H, 5.30; N, 5.66%). (Found M+, 247.0685 $C_{13}H_{13}NO_2S$ requires 247.0684).

ν_{max}(film)/cm^{-1} 3301 (N-H), 1671, 1585, 1554 (C=C); δ_H(300MHz, $CDCl_3$) 7.90 (2H, d, *J*=8.1, ***H***-Ar), 7.65-7.51 (3H, m, ***H***-Ar), 7.30-7.20 (5H, m, ***H***-Ar), 4.73 (1H, br, N***H***), 4.17 (2H, d, *J*=6.2, CH_2); δ_C(75MHz, $CDCl_3$) 140.27, 136.51, 133.13, 129.55, 129.13, 128.39, 128.26and 127.51 (***C*** of 2Ar), 47.71 (***C***H_2); ***m/z*** (CI) 248 (M^++1, 16%), 106 (100), 91 (37), 77 (21).

7.6.4. General procedure for the preparation of N-alkyl-N-tosyl trichloroacetamides

n-BuLi (1.6M in hexane) was added to a solution of N-alkenyl or N-alkyl-N-tosylamide in diethyl ether at –78 °C and the solution was stirred at this temperature for30 min. Trichloroacetyl chloride was added and the mixture was stirred for 2 hours. Excess base was quenched with saturated aqueous NH_4Cl and the mixture was quickly extracted with diethyl ether (3x50ml). The extracts were washed with 1N NaOH and 1N NaCl, dried and concentrated.

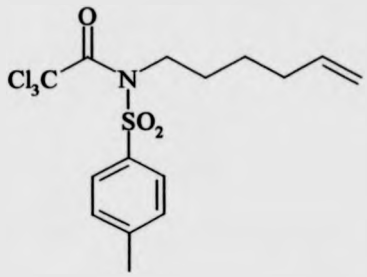
7.6.4.1. N-Pent-4-enyl-N-tosyl trichloroacetamide [213a]



N-Pent-4-enyl-N-tosylamide (0.4g, 1.7mmol) in ether (30ml) was reacted with n-BuLi (1.10ml, 1.7mmol) them with trichloroacetyl chloride (0.31g, 1.7mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-pent-4-enyl-N-tosyl trichloroacetamide (403mg, 63%) as white solid, 70-71 °C. (Found: C, 43.66; H, 4.22; N, 3.47%. Calc. for $C_{14}H_{16}NO_3SCl_3$: C, 43.71; H, 4.19; N, 3.64%). (Found M+, 382.9933 $C_{14}H_{16}NO_3SCl_3$ requires 382.9933).

ν_{max}(film)/cm^{-1} 1713 (C=O), 1662, 1556 (C=C); δ_H(300MHz, $CDCl_3$) 7.92 (2H, d, *J*=8.4, ***H***-Ar), 7.36 (2H, d, *J*=8.4, ***H***-Ar), 5.88-5.76 (1H, m, C***H***=CH_2), 5.15-5.05 (2H, m, CH=C***H₂***), 4.24-4.17 (2H, m, C***H₂***-N), 2.47 (3H, s, C***H₃***), 2.19-2.10 (4H, m, 2x C***H₂***); δ_C(75MHz, $CDCl_3$) 157.17 (***C***=O), 145.97 (1***C*** of Ar), 136.98 (***C***H=CH_2), 135.18, 129.90 and 129.54 (5***C*** of Ar), 116.37 (CH=***C***H_2), 102.50 (***C***Cl_3), 49.50 (***C***H_2-N), 31.23 and 29.69 (2C of 2x***C***H_2), 22.14 (***C***H_3); ***m/z*** (CI) 384 (M^++1, 65%), 155 (100), 108 (85), 91 (79).

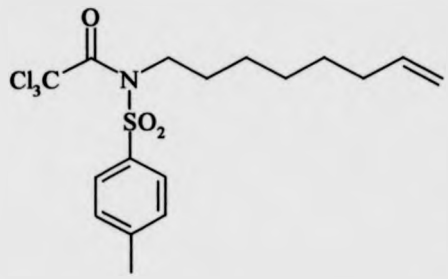
7.6.4.2. N-Hex-5-enyl-N-tosyl trichloroacetamide [213b]



N-Hex-4-enyl-N-tosylamide (0.16g, 0.65mmol) in ether (30ml) was reacted with n-BuLi (0.4ml, 0.65mmol) then with trichloroacetyl chloride (0.12g, 0.65mmol) Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-hex-5-enyl-N-tosyl trichloroacetamide (210mg, 81%) as white solid, 73-74 °C. (Found: C, 44.78; H, 4.56; N, 3.15%. Calc. for $C_{15}H_{18}NO_3SCl_3$: C, 45.18; H, 4.55; N, 3.51%). (Found M+, 397.0085 $C_{15}H_{18}NO_3SCl_3$ requires 397.0090).

ν_{max}(film)/cm^{-1} 1712 (C=O), 1552 (C=C); δ_H(300MHz, $CDCl_3$) 7.89 (2H, d, *J*=8.3, ***H***-Ar), 7.32 (2H, d, *J*=8.3, ***H***-Ar), 5.85-5.72 (1H, m, C***H***=CH_2), 5.06-4.96 (2H, m, CH=C***H₂***), 4.20-4.15 (2H, m, C***H₂***-N), 2.44 (3H, s, C***H₃***), 2.14-2.07 (2H, m, ***C***H_2-CH=), 2.04-1.94 and 1.49-1.40 (4H, m, 2x C***H₂***); δ_C(75MHz, $CDCl_3$) 157.17 (***C***=O), 145.97 (1***C*** of Ar), 136.98 (***C***H=CH_2), 135.18, 129.90 and 129.54 (5***C*** of Ar), 116.37 (CH=***C***H_2), 104.60 (***C***Cl_3), 49.50 (***C***H_2-N), 33.04, 29.94 and 25.86 (3x***C***H_2), 22.14 (***C***H_3); ***m/z*** (CI) 398 (M^++1, 71%), 155 (100), 108 (80), 91 (62).

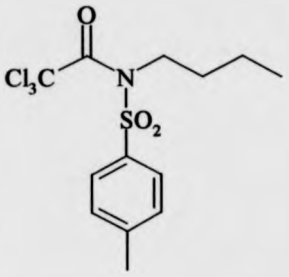
7.6.4.3. N-Oct-7-enyl-N-tosyl trichloroacetamide [213c]



N-Oct-7-enyl-N-tosylamide (0.37g, 1.3mmol) in diethyl ether (20ml) was reacted with n-BuLi (0.85ml, 1.3mmol) then with trichloroacetyl chloride (0.24g, 1.3mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-oct-7-enyl-N-tosyl trichloroacetamide (457, 81%) as white solid, mp 50-51 °C. (Found: C, 47.96; H, 5.24; N, 3.05%. Calc. for $C_{17}H_{22}NO_3SCl_3$: C, 47.84; H, 5.20; N, 3.20%). (Found M+, 425.0405 $C_{17}H_{22}NO_3SCl_3$ requires 425.0403).

ν_{max}(film)/cm^{-1} 1714 (C=O), 1610, 1552 (C=C); δ_H(300MHz, $CDCl_3$) 7.48 (2H, d, *J*=8.4, ***H***-Ar), 7.32 (2H, d, *J*=8.4, ***H***-Ar), 5.86-5.73 (1H, m, C***H***=CH_2), 5.02-4.92 (2H, m, CH=C***H₂***), 4.18-4.13 (2H, m, C***H₂***-N), 2.44 (3H, s, C***H₃***), 2.06-1.95 (4H, m, 2x CH_2), 1.42-1.29 (6H, m, 3x C***H₂***); δ_C(75MHz, $CDCl_3$) 157.70 (***C***=O), 145.49 (1***C*** of Ar), 138.78 (***C***H=CH_2), 134.87, 129.47 and 129.13 (5***C*** of Ar), 114.48 (CH=***C***H_2), 101.73 (***C***Cl_3), 49.52 (***C***H_2-N), 33.58, 30.42, 28.72, 28.46 and 26.47 (5C of ***C***H_2), 21.73 (***C***H_3); ***m/z*** (Cl) 426 (M^++1, 100%), 358 (47), 155 (90), 108 (83), 91 (72).

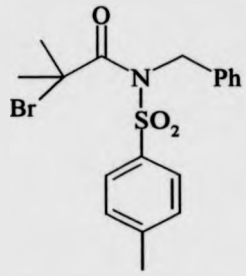
7.6.4.4. N-(n-Butyl)-N-tosyl trichloroacetamide [213d]



N-(n-Butyl)-N-tosylamide (2.16g, 10mmol) in diethyl ether (50ml) was reacted with n-BuLi (6.25ml, 10mmol) then with trichloroacetyl chloride (1.90g, 10mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-(n-butyl)-N-tosyl trichloroacetamide (2.76g, 73%) as white solid; mp 90-91 °C. (Found: C, 42.28; H, 4.42; N, 3.55%. Calc. for $C_{13}H_{16}NO_3SCl_3$: C, 41.90; H, 4.33; N, 3.76%). (Found M+, 370.9933 $C_{13}H_{16}NO_3SCl_3$ requires 370.9933).

ν_{max}(film)/cm^{-1} 1710 (C=O), 1596 (C=C); δ_H(300MHz, $CDCl_3$) 7.89 (2H, d, *J*=8.4, ***H***-Ar), 7.32 (2H, d, *J*=8.4, ***H***-Ar), 4.20-4.14 (2H, m, C***H***$_2$-N), 2.43 (3H, s, C***H***$_3$-Ar), 2.01-1.90 and 1.44-1.26 (4H, m, 2x C***H***$_2$), 0.97 (3H, t, *J*=7.3, C***H***$_3$); δ_C(75MHz, $CDCl_3$) 159.21 (***C***=O), 145.89, 135.29, 129.87 and 129.54 (6***C*** of Ar), 49.76 (***C***H_2-N), 32.83 (***C***H_2), 22.14 (***C***H_3-Ar), 20.31 (***C***H_2), 13.99 (***C***H_3); ***m/z*** (CI) 372 (M^++1, 100%), 155 (80), 91 (50).

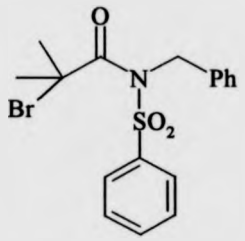
7.6.4.5. N-Benzyl-N-tosyl-(2-bromo-2-methyl) propamide [226a]



N-Benzyl-N-tosylamide (0.350g, 1.9mmol) in diethyl ether (20ml) was reacted with n-BuLi (1.2ml, 1.9mmol) then with 2-bromoisobutyryl bromide (0.44g, 1.9mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-benzyl-N-tosyl-(2-bromo-2-methyl) propamide [226a] (610mg, 78%) as white solid; mp 120-122 °C. (Found: C, 52.65; H, 4.99; N, 3.23%. Calc. for $C_{18}H_{20}NO_3SBr$: C, 52.69; H, 4.91; N, 3.43%). (Found M+, 409.0366 $C_{18}H_{20}NO_3SBr$ requires 409.0364)

ν_{max}(film)/cm^{-1} 1668 (C=O), 1595, 1495, 1443 (C=C); δ_H(300MHz, $CDCl_3$) 7.62 (2H, d, *J*=7.7, ***H***-Ar), 7.32-7.18 (7H, m, ***H***-Ar), 5.54 (2H, s, C***H*****$_2$**), 2.40 (3H, s, C***H*****$_3$**-Ar), 1.86 (6H, s, 2 x C***H*****$_3$**); δ_C(75MHz, $CDCl_3$) 174.20 (***C***=O), 129.41, 129.04, 127.96 and 127.10 (12 ***C*** of 2Ar), 57.50 (***C***Me_2Br), 52.46 (***C***H_2), 32.43 (2 x' ***C***H_3), 22.06 (***C***H_3-Ar); ***m/z*** (CI) 410 (M^++1, 75%), 332 (27), 268 (100), 106 (32), 91 (25).

7.6.4.6. N-Benzenesulfonyl-N-benzyl-(2-bromo-2-methyl) propamide [226b]



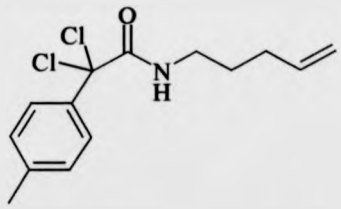
N-Benzyl-N-bezenesulfonylamide (0.50g, 2mmol) in diethyl ether (20ml) was reacted with n-BuLi (1.25ml, 2mmol) then with 2-bromoisobutylryl bromide (0.47g, 2mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the N-benzenesulfonyl-N-benzyl-(2-bromo-2-methyl) propamide [226b] (610g, 76%) as white solid, mp 113-114 °C. (Found: C, 51.48; H, 4.81; N, 3.33%. Calc. for $C_{17}H_{18}NO_3SBr$: C, 51.52; H, 4.58; N, 3.53%). (Found M+, 395.0203 $C_{17}H_{18}NO_3SBr$ requires 395.0208).

ν_{max}(film)/cm^{-1} 1687 (C=O), 1549, 1496, 1448 (C=C); δ_H(300MHz, $CDCl_3$) 7.75-7.21 (10H, m, ***H***-Ar), 5.56 (2H, s, C***H₂***), 1.87 (6H, s, 2x C***H₃***); δ_C(75MHz, $CDCl_3$) 171.60 (C=O), 139.19, 136.73, 133.95, 129.47, 129.32, 129.07, 128.26 and 127.12 (12***C*** of 2Ar), 57.43 (***C***Me_2Br), 52.53 (***C***H_2), 32.40 (2 x ***C***H_3); ***m/z*** (CI) 396 (M^++1, 16%), 316 (25), 254 (100), 91 (30), 77 (12).

7.6.5.General procedure for the rearrangement

N-alkenyl-N-tosyl trichloroacetamide (1eq.) and CuCl (1eq.) were stirred under nitrogen for 30 minutes. Solvent was then added and solution of ligand [209] (1eq) in solvent (1ml) was added immediately. The mixture was stirred for 24 hours at room temperature. The resulting mixture was eluted through a short silica gel column with dichlorometane. The mixture of starting acetamide, reduced product and rearrangement product was obtained as a yellow oil.

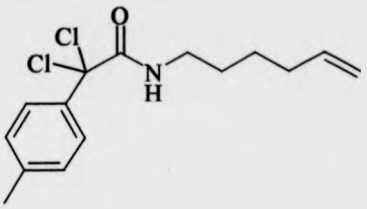
7.6.5.1. N-Pent-4-enyl-(2,2-dichloro-*p*-toluene) acetamide



N-Pent-4-enyl-N-tosyl trichloroacetamide (170mg, 0.43 mmol) was reacted in the presence of CuCl (43mg, 0.43mmol) and ligand [209] (76mg. 0.43mmol). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the mixture of N-pent-4-enyl-(2,2-dichloro-*p*-toluene) acetamide and the corresponding reduced product which could not be fully separated in 25 mg (ratio 90:10) as a yellow oil.

ν_{max}(film)/cm^{-1} 3438 (N-H), 1720 (C=O), 1517 (C=C); δ_H(300MHz, $CDCl_3$) 7.57 (2H, d, *J*=8.2, ***H***-Ar), 7.19 (2H, d, *J*=8.2, ***H***-Ar), 6.81 (1H, br, N***H***), 5.82-5.87 (1H, m, C***H***=CH_2), 5.11-4.97 (2H, m, CH=C***H₂***), 3.35 (2H, q, *J*=5.9, C***H₂***-N), 2.35 (3H, s, C***H₃***), 2.13-2.05 (4H, m, 2 x C***H₂***); δ_C(75MHz, $CDCl_3$) ; ***m/z*** (CI) (M^++1,%) 160.05 (***C***=O), 140.00 (1***C*** of Ar), 137.79 (***C***H=CH_2), 137.64, 129.49 and 126.87 (5***C*** of Ar), 116.06 (CH=***C***H_2), 65.20 (***C***Cl_2Ar), 40.91 (***C***H_2-N), 31.40 and 28.54 (2C of 2x***C***H_2), 21.51 (***C***H_3).

7.6.5.2. N-Hex-5-enyl-(2,2-dichloro-*p*-toluene) acetamide

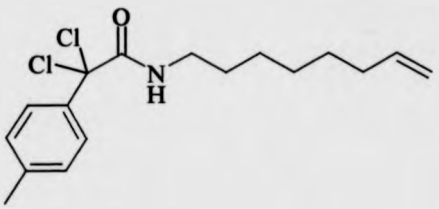


N-Hex-5-enyl-N-tosyl trichloroacetamide (150mg, 0.37 mmol) was reacted in the present of CuCl (37mg, 0.37mmol) and ligand [209] (65mg. 0.37mmol) in dichloromethane (3.3ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the mixture of N-hex-5-enyl-(2,2-dichloro-*p*-toluene) acetamide and the corresponding reduced product which could not be fully separated in 65 mg (ratio 50:50) as a yellow oil .

ν_{max}(film)/cm^{-1} 3410 (N-H), 1708 (C=O), 1612 (C=C); δ_H(300MHz, $CDCl_3$) 7.50 (2H, d, *J*=8.5, ***H***-Ar), 7.12 (2H, d, *J*=8.5, ***H***-Ar), 6.74 (1H, br, N***H***), 5.77-5.60 (1H, m, C***H***=CH_2), 4.96-4.86 (2H, m, CH=C***H₂***), 3.30-3.24 (2H, m, C***H₂***-N), 2.28 (3H, s,

C***H₃***), 2.03-1.93 (2H, m, ***C***H₂-CH=), 1.61-1.46 and 1.39-1.18 (4H, m, 2x C***H₂***), δ_C(75MHz, $CDCl_3$) 165.50 (***C***=O), 140.38 (1***C*** of Ar), 138.56 (***C***H=CH₂), 130.62 and 128.20 (5***C*** of Ar), 115.45 (CH=***C***H₂), 65.26 (***C***Cl₂Ar), 48.10 (***C***H₂-N), 33.57, 28.91 and 26.32 (3x***C***H₂), 22.12 (***C***H₃); ***m/z*** (CI) 300 (M^++1, 28%), 266 (50), 232 (100).

7.6.5.3. N-Oct-7-enyl-(2,2-dichloro-*p*-toluene) acetamide

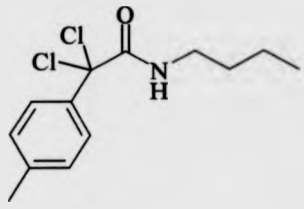


N-Oct-7-enyl-N-tosyl trichloroacetamide (370mg, 0.88 mmol) was reacted in the present of CuCl (87mg, 0.88mmol) and ligand [209] (155mg, 0.88mmol) in dichloromethane (7.8ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded the mixture of N-oct-7-enyl-(2,2-dichloro-*p*-toluene) acetamide and the corresponding reduced product which could not be fully separated in 127 mg (ratio 41:59) as a yellow oil .

ν_{max}(film)/cm^{-1} 3400 (N-H), 1708 (C=O), 1640,1596, 1462 (C=C); δ_H(300MHz, $CDCl_3$) 7.30 (2H, d, *J*=8.2, ***H***-Ar), 7.12 (2H, d, *J*=8.2, ***H***-Ar), 6.73 (1H, br, N***H***) 5.76-5.64 (1H, m, C***H***=CH₂), 4.96-4.84 (2H, m, CH=C***H₂***), 3.25 (2H, t, *J*= 7.1, C***H₂***-N), 2.29 (3H, s, C***H₃***), 1.96-1.91 (2H, m, ***C***H₂-CH=), 1.56-1.47 (2H, m, C***H₂***), 1.30-1.19 (6H, m, 3x C***H₂***), δ_C(75MHz, $CDCl_3$) 165.80 (***C***=O), 146.30 (1***C*** of Ar), 139.22 (***C***H=CH₂), 137.16, 129.53, 128.19 and 126.85 (5***C*** of Ar), 114.48 (CH=***C***H₂), 60.78

(CCl_2Ar), 49.91 (CH_2-N), 30.81, 29.43, 29.08, 29.00 and 26.94 (5C of CH_2), 21.49 (CH_3); *m/z* (CI) 328 (M^++1, 30%), 260 (100), 106 (52), 912 (79).

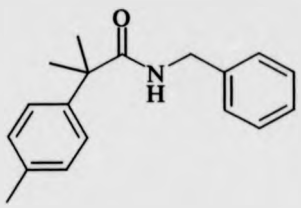
7.6.5.4. N-(n-Butyl)-(2,2-dichloro-*p*-toluene) acetamide



N-(n-butyl)-N-tosyl trichloroacetamide (500mg, 1.34 mmol) was reacted in the present of CuCl (133mg, 1.34mmol) and ligand [209] (317mg, 1.34mole) in dichloromethane (12ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-(n-butyl)-(2,2-dichloro-*p*-toluene) acetamide in (307mg, 84%) as a yellow oil. (Found MH+ 274.0774, $C_{13}H_{18}NOCl_2$ requires 274.0765).

ν_{max}(film)/cm^{-1} 3343 (N-H), 1680 (C=O), 1612, 1517, 1454 (C=C); δ_H(300MHz, $CDCl_3$) 7.49 (2H, d, *J*=8.4, ***H***-Ar), 7.10 (2H, d, *J*=8.4, ***H***-Ar), 6.81 (1H, br, N***H***), 3.23 (2H, t, *J*=6.6, C***H₂***-N), 2.26 (3H, s, C***H₃***-Ar), 1.50-1.40 and 1.31-1.16 (4H, m, 2x C***H₂***), 0.83 (3H, t, *J*=7.3, C***H₃***); δ_C(75MHz, $CDCl_3$) 165.28 (***C***=O), 139.70, 136.60, 128.85 and 126.24 (6***C*** of Ar), 86.69 (CCl_2Ar), 40.55 (CH_2-N), 30.92 (CH_2), 20.88 (CH_3-Ar), 19.73 (CH_2), 13.49 (CH_3); *m/z* (CI) 274 (M^++1, 97%), 238 (100), 210 (36).

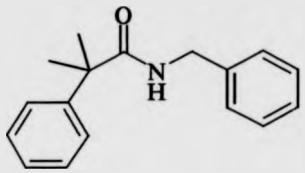
7.6.5.5. N-Benzyl-(2-methyl-2-*p*-toluene propamide [228a]



N-benzyl-N-tosyl-N-2-bromoisobutylrylacetamide (129mg, 0.31mmol) was reacted in the present of CuBr (44.5mg, 0.31mmol) and ligand [209] (71.3mg. 0.31mole) in dichloromethane (2.8ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-benzyl-(2-methyl-2-*p*-toluene propamide [228a] (10mg, 10%) as a light yellow solid; mp 170-171 °C. (Found: C, 80.50; H, 7.56; N, 4.82%. Calc. for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24%). (Found M^+ 267.1619, $C_{18}H_{21}NO$ requires 267.1623).

ν_{max}(film)/cm^{-1} 3435 (N-H), 1675 (C=O), 1504, 1453 (C=C); δ_H(300MHz, $CDCl_3$) 7.36-7.10 (9H, m, ***H***-Ar), 5.43 (1H, m, N***H***), 4.45 (2H, d, *J*=5.8, C***H***$_2$), 2.31 (3H, s, C***H***$_3$-Ar), 1.58 (6H, s, 2x C***H***$_3$); δ_C(75MHz, $CDCl_3$) 164.54 (***C***=O), 145.07, 138.94, 136.22, 129.81, 129.45, 128.56, 127.71 and 126.77 (12 ***C*** of 2Ar), 57.55 (***C***Me$_2$Ar), 43.96 (***C***H$_2$), 27.54 (2 x ***C***H$_3$), 21.35 (***C***H$_3$-Ar); ***m/z*** (EI) 267 (M^+, 23%), 133 (100), 119 (44), 105 (38), 91 (47).

7.6.5.6. N-Benzyl-(2-methyl-2-phenyl) propamide [228b]



N-benzyl-N-benzenesulfonyl-N-2-bromoisobutylrylacetamide (130mg, 0.33mmol) was reacted in the present of CuBr (47mg, 0.33mmol) and ligand [209] (76mg. 0.33mole) in dichloromethane (3ml). Purification by silica gel column chromatography (petroleum ether: ethyl acetate, 5:1) afforded N-benzyl-(2-methyl-2-phenyl) propamide [228b] in (10mg, 9%) as a light yellow solid; 155-157 °C. (Found: C, 80.56; H, 7.39; N, 5.17%. Calc. for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.13%). (Found M^+ 253.1466, $C_{17}H_{19}NO$ requires 253.1466).

ν_{max}(film)/cm^{-1}3436 (N-H), 1675 (C=O), 1600, 1505, 1454 (C=O); δ_H(300MHz, $CDCl_3$) .58-7.09 (10H, m, ***H***-Ar), 5.52 (1H, br, N***H***), 4.36 (2H, d, *J*=5.8, C***H***$_2$), 1.60 (6H, s, 2x C***H***$_3$); δ_C(75MHz, $CDCl_3$) 163.93 (C=O), 145.42, 129.12, 128.97, 127.72, 127.67, 127.45 and 126.82 (12*C* of 2Ar), 52.08 (*C*Me$_2$Ar), 43.97 (*C*H$_2$), 27.50 (2 x *C*H$_3$); ***m/z*** (EI) 253 (M^+, 14%), 119 (74), 91 (100), 41 (39).

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